The Treatment of

Diabetes Mellitus

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The Treatment of

DIABETES MELLITUS

Tenth Edition, Revised, Illustrated

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TO

ALL THOSE

WHO BY THEIR GIFTS GREAT AND SMALL

HAVE MADE POSSIBLE

CAMPS FOR DIABETIC CHILDREN

INSTRUCTION IN DIABETES

FOR

PATIENTS, THEIR FAMILIES, NURSES, PHYSICIANS

AND

THE CREATION OF THE HOSPITAL TEACHING CLINIC

AND

THE FURTHERANCE OF RESEARCH

PREFACE TO THE TENTH EDITION

This edition is a partial fulfillment of a duty owed to patients, physicians and Boards of Health who have helped us to report the results of treatment. The treatment of diabetes, although still grossly inadequate, is steadily

Recent methods of treatment have not led us to discard the old, but have made the old more practical and less costly We must do more to reduce expense, and somehow or other bring it about that a diabetic adult is contacted every three months and children every four weeks Taking account of stock once a year may suffice in business, but not in diabetes, knowing the old and planning the new must take place more often than once in twelve months

As for the oral treatment of diabetes our experience, with at least 3000 patients so treated, is recorded The oral drugs have given fresh hope to the patients and have been convenient particularly in the older ones with deficient eyesight No one claims them to be equal to insulin and as yet there is no final conclusion as to their mode of action Their incidental contributions to the patient have been an added respect for insulin and the need for closer adherence to the diet, and for the doctor, the opening up of many new pathways for research

Prevention of diabetes, or at least the deferment of its onset and its complications, is now the goal for which everyone is striving Boulin crystallized the idea by opening his pre-diabetic clinic in Paris Prevention takes precedence over heredity One in three or four in the country has a diabetic relative and one cannot prevent 60,000,000 people getting married In the course of one week at the Boston Lying-In Hospital 9 diabetic mothers had 11 healthy children, and among them 2 sets of twins on the same day

The literature on diabetes is overwhelming We regret the omission of references to important contributions In the periodical *Diabetes* alone there have been some 300 leading articles and 3000 abstracts in the six years since 1952 when our ninth edition was published

The means for treatment of the diabetic are more adequate than ever,

appeared when treatment has been neglected or delayed The data are

based on a total of 52,560 patients who have consulted us. Deaths from coma have fallen from 64 per cent to 1.0 per cent and from tuberculosis to 0.2 per cent of the total, although each of these complications once was a major cause of death. Indeed deaths from gangrene have also declined to about 1 per cent, although the problems of the care of lesions of the lower extremities have multiplied, since patients live so long and need so much rehabilitation. Cardiovascular-renal disease has replaced former causes of death, reaching 77 per cent. When we began treating diabetics, coma and tuberculosis seemed more hopeless than does today the possibility of a cure or postponement of premature cardiovascular-renal disease.

The complications of diabetes, our methods of attack upon them, and our results occupy a large share of the book—and why? Virgil wrote, "Mortui vivos docent." As a result of our 18055 fatalities we have gradually accumulated data which compel us to state unequivocally, that of those complications, which have ravaged our diabetics, most can be explained by failure to control the disease. One still reads that retinitis, nephropathy and neuritis bear no relation to control, but our detailed investigation of diabetics who have come under our own supervision proves the contrary.

The treatment of the uncomplicated disease, diabetes itself, is simple enough provided the patient understands and follows the rules. Success depends upon continual control. Most any diabetic, young or old, will live ten years today with a moderate restriction of diet plus insulin, but therein lies the danger. Conclusions are unwarranted unless they are computed and analyzed, based upon a duration of three, four, even five decades following the onset of the disease. For this reason the chapter on children bears the title "Diabetic Children and Their Later Lives," because most of a diabetic child's life is lived as an adult. From studies begun with children, with adolescents and young adults, we know others like ourselves are convinced that with strict control of the disease headway is being made toward the abolition of that needless triopathy—neuritis, retinitis, nephritis. The measures used to conquer coma and tuberculosis were relatively simple, but to overcome neuritis, nephritis, retinitis and cardiovascular degeneration one must depend upon diet, exercise, insulin and education but, above all else, upon control of the human nature of the patient. With a missionary's zeal one must convert not alone his mind and soul but also his doctor, to the realization that it is worth the effort to control the disease as shown by a sugar-free urine, normal blood sugar and cholesterol.

Diabetic camps taught us a great lesson. Our children, who have died in the last few years, have lived twenty-six years instead of two years. But today a study of these longer living diabetics shows they needed more opportunities for postgraduate education and rehabilitation. This became so urgent that we have the Hospital Teaching Clinic to which ambulatory patients can return for a few days for a review of their condition and at reduced rates, brought about by concentration of teaching and the shortening of hospital stay. By no means are we alone in such undertakings and it is fortunate that different methods are being tried in various areas of this country and the world with the same purpose in mind.

In 1948 we knew of but one patient who had had the disease twenty-five years and was perfect. This qualified him for the Quarter Century Victory Medal of the Boston Safe Deposit and Trust Company which was designed by Amelia Peabody. Today there are 82 such patients. As yet we have not seen a diabetic with the disease uncontrolled for twenty-five years who could meet the criteria. Have you? The time should come when diabetics will even outlive their contemporaries, because of their better hygiene and closer medical supervision by which conditions, bearing no relation to diabetes, will be discovered earlier and remedied and thus overcome the handicap of the diabetes.

To so many we are indebted in the compilation of the Tenth Edition. To Doctors Warren and LeCompte for the Chapter on the Pathology, to Dr. Nancy Nichols for clarifying the mineral metabolism, to Dr. Renold for his Chapter on Physiology and his studies and comments on our prize remission diabetic with the normal blood sugar lowering component in the blood and to Dr. Schwartz and Dr. Renold for their Table and description of 12 cases of lipo-atrophic diabetes. Our colleagues Dr. Krall and Dr. Bradley have helped much by their contributions to the text and Dr. Allen Joslin by caring for patients so that we all could be authors.

Many secretaries have helped us but had we not had the benefit of the painstaking supervisory assistance of Miss Anna C. Holt, for thirty-five years at the Library of the Harvard Medical School, the book could not have been completed this year. As formerly every courtesy has been extended to us by our publishers, Messrs. Lea & Febiger to whom we are most grateful.

ELLIOTT P. JOSLIN, HOWARD F. ROOT
PRISCILLA WHITE, ALEXANDER MARBLE

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The Treatment of
DIABETES MELLITUS

Chapter 1

PRESENT CONCEPTS OF DIABETES

ELLIOTT P. JOSLIN, M.D

PREVENTION of diabetes today demands priority in any consideration of the disease The salient facts emphasizing this responsibility are, (*a*) the rapidly increasing number of diabetics, of whom many live longer than formerly, (*b*) their great fecundity, permitting the transmission of a hereditary gene, (*c*) the aging of the population into the fifth and sixth decades when onset of the disease is most common, (*d*) the lessening of the need for physical work and the abundance of food consumed with resulting obesity, and finally (*e*) the earlier detection and more aggressive treatment both of the mild and severe case gives a better opportunity for control of the disease

The prevention or the deferment of onset and the control of diabetes are within the range of possibility because of our better knowledge of the long pre-diabetic state in the great majority of cases, and the means for earlier detection and control of the disease, even when the onset is acute, by [illegible]

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irreversible Animal experimentation has demonstrated the opposite Consider our own borderline unclassified glycosuria cases, 1946 of them, whom Dr Marble traced and after about ten years found only 9 9 per cent had become diabetic These were the ones in whom obesity, heredity and the Jewish race were predominant No claim to have cured a diabetic is made, but may not frank diabetes have been so postponed in many of the remaining 90 per cent that it has not yet become manifest? No longer should we say, "*Le médecin arrive trop tard*"

Today, these remissions of diabetes early in its course in which the pancreas is *rested* are one of the most hopeful features of the disease Undoubtedly, Bouchardat recognized the same, because of his remark that in no disease was a relapse more common, Cantani felt the same about control, and so did Naunyn when he pointed out that the apparently

severe diabetic treated aggressively often later surprised one by being mild. As soon as insulin came, we recognized that the units could be decreased soon after onset. We never advised the omission of insulin even if only one unit, because we felt so sure the disease would return and we did not want to give false hopes to the patients by the omission and later resumption of insulin. Now with these remissions more in mind we recognize they occur in old as well as in young diabetics, and that this period for the disease presents a golden opportunity for treatment which may never return (Brush) What brings these remissions about? Must they always be transitory? Can they not be prolonged for weeks, months, years or a lifetime? Case 50845, a girl of 19, with a probable onset of diabetes in October but first seen in December 1957, was rescued from coma with 1600 units of insulin December 4-15, 1957, at the Norwood Hospital by Doctors Buckley, Cadigan and Sieracki and later seen by us January 9, 1958, with the urine sugar free and receiving 45 units of insulin In the course of a week she was aglycosuric and with normal glycemia The blood sugar fasting was 90 mg, and 64 mg at 11 A M with 4 units of insulin and carbohydrate 180, protein 90, fat 90 grams Upon January 23, Dr Martin and Dr Renold found twice the usual insulin-like activity material in the blood, 300 micro-units per milliliter The 4 units of insulin were continued but omitted on February 6 and 7, and on February 8 the test for the insulin-like material was repeated and was 150 microunits per milliliter The urine was sugar free and the capillary blood sugar after breakfast was 177 mg The urine continued to be sugar free with 4 units of insulin daily On March 29, the test was repeated and was 50 mg microunits per milliliter The urine contained 0 1 per cent sugar. This was following a

remained in good condition, with a blood sugar of 133 mg and glycosuria 1 3 per cent one hour after breakfast

The significance of the sugar-lowering material in the blood, following a period in which 1600 units of insulin were necessary to rescue the patient is certainly important If there are two types of diabetes juvenile and adult to which does this patient belong? Might there not be one type with two manifestations? Should not the aggressive treatment at the beginning of her disease in some fashion be continued? Is progress into the full diabetic status inevitable? Why not continue the Brush treatment of rest for the pancreas? That is our intention As for the significance of these findings, time alone will tell

How many diabetics are there in the United States in 1958? The most reliable source of information in our opinion is that based upon the investigation of the number of cases in the town of Oxford, Massachusetts by Wilkerson and Krall There it was demonstrated by examinations of the urine and blood of the inhabitants of this typical American town that the prevalence was 1 7 per cent Using this figure for the 172,830,000 people in the United States at the end of 1957, we have approximately 2,950,000 individuals or about 3,000,000 people in the United States with diabetes

Excellent data were contributed as a result of a National Health Survey

and those of insurance companies are of great value. Errors in estimates based upon death certificates occur because the word "diabetes," for various reasons, does not appear on the certificate Thus, in 1936 and ... at at ... was

Consequently, whenever one sees a statistical report of diabetes based on death certificates as a cause of death, add one-half to it to arrive at a more accurate incidence of diabetes in the community

Diabetes at the beginning of the century ranked twenty-seventh as a cause of death, but now is eighth for the United States and fifth in the statistics of the Metropolitan Life Insurance Company. The life insurance companies have sensed the change in the status of diabetes In 1940, there was but one insurance company in the United States and Canada offering insurance to diabetics Now over 75 per cent of all insurance companies insure them, and with continually liberalizing policies Along with the increasing duration of life and growing health of diabetics, their ability for employment is more and more being utilized

The causes for death of diabetics have changed so remarkably that it radically alters plans for the management of the disease Tuberculosis which undoubtedly was responsible for the death of half the patients fifty years, or even a generation ago in many large city hospitals, has now dropped to 0 2 per cent Diabetic coma has fallen from 64 per cent to 1 per cent, but vascular disease in the heart, brain and kidneys is now responsible for at least 75 per cent of the deaths Gangrene has dropped to 1 per cent, but its cost is still enormous and estimated at a million dollars yearly in the Boston area alone For the children complications in the kidney are steadily mounting to be the chief foe Due to the longer lives of diabetics, cancer has risen to 11 3 per cent Now we know by our own studies that it bears no relation to diabetes Cancer should be discovered earlier in these patients and treated better because they are under closer medical supervision

The possible influence of heredity is startling On January 21, 1958, a woman, case 50888, came to me with diabetes. She had had 14 children, 8 now alive On the following day another woman came who had 13 children and whose husband was a diabetic Case 51193, came on March 13, 1958, with diabetes of twenty-three years duration Her twin brother, one sister and her parents have it and one brother died of it. Recently,

Research has been greatly advanced by studies upon the pregnant diabetic woman. According to Bouchardat she was to him an unknown *In the early years of the present century she was rarely seen, although the*

such a glycosuria was denominated renal in character. The few diabetic women who became pregnant died of coma and only exceptionally bore a living, healthy child until the advent of the Allen undernutrition era. In 1914, pregnancy was countenanced for a young diabetic who carried through with success and the healthy child is now forty-four years old. In 1915, a doctor's wife, remained three months in the hospital and also

Priscilla White with our growing girls began her series which now numbers about 2000. Upon January 21,

career and her infants we have learned much If the baby weighs 13 pounds, 90 per cent of the mothers will develop diabetes and if 14 pounds, 100 per cent Hoet has pointed out that pregnancy makes it possible by a glucose tolerance test to diagnose a latent diabetes, which is not demonstrated when the pregnancy is over Wilkerson on a large scale has data *which suggest that if a diabetes is actively treated and the weight of the* child restricted the mother may be protected from a subsequent immediate diabetes Jackson found that diabetic fathers have big babies though there is no increase in fetal mortality The obstetrician now, as a matter of course, plans to terminate early, often by Cesarean section a diabetic

leagues hope that *her utilization of hormones is responsible for her good results and not alone her diabetic and clinical acumen The pregnant*

times as liable to have diabetes a
are far more common

For advice as to pregnancy the importance of the family doctor is paramount because upon him will depend *the care of mother and child* after delivery He can influence the number of future diabetics and by his advice against the marriage of one diabetic to another, halt the develop-

ment of obesity, particularly in the relatives of diabetics before the age of forty years is reached, and is the one who profitably and inexpensively can discover new cases by examining the urine and blood of the relatives of

ment of the disease when established, the responsibility for its continuous control rests with the family physician

Children form a far more important part of the diabetic population now than in the Naunyn Era Of the 4219 in our group with onset under the age of fifteen years, we know 3352 are alive. Of those in the first decade of onset succumbing to the disease, 1897–1914, the duration of life was 1.2 years but recently has been twenty-six years It is true that all diabetics are living longer, but diabetic children now have the longest duration of life of all ages of diabetics and demand proportionately more attention The average duration of life of all diabetics of all ages who have died recently has risen from 4 9 years to 18 2 years

The dietetic treatment of the diabetic in one way is simplified, because we know so much more about diet and insulin The diet should contain daily at least 150 grams of carbohydrate, 1 gram of protein per kilogram body weight with adjustment for growth requirements, and fat sufficient to furnish adequate calories for maintenance of vigor and growth Whether more carbohydrate than 200 grams daily should be allowed any diabetic, save for unusual exercise, time alone can tell A limitation to 200 grams carbohydrate daily may involve the necessity of giving excessive quantities of protein and fat

wait for more unanimously positive advice from our nutrition specialists

Exercise in the days before insulin we regarded as useful, but by no means did we appreciate that it was as vital in the care of diabetics as Bouchardat taught We should return to it to help us in the treatment of

useful if vigorous enough to bring on sweating Best of all, insert exercise into the daily routine

Control of diabetes pays. This I know. Case No 8, developed diabetes in 1899, at the age of sixty years, and from Naunyn I learned how to treat her. She never broke her diet and lived out her full life expectancy. Similar cases early came to my attention and proved to me that the better the treatment is carried out the greater the happiness and comfort for the [illegible]

Medal, and especially the 82 who have received our Quarter Century Diabetic Victory Medal In general these were the ones who took great pains with the control of their diabetes. Our first Victory Medal patient, S.R., had everything to help him, financial resources, parents, an experienced nurse for seven years and a cooperative [illegible] He taught us that we should build the [illegible] others who were less fortunate a chance [illegible] surmounted unusual trials and deserve recognition, yet because of their battle scars are not physically perfect, we should award citations like those given in the armed forces for unusual valor

Because of close control pregnant diabetics seldom die and of 84 diabetics with tuberculosis under treatment, only one died in a year and that death was not due to tuberculosis[1]

Control of diabetes is necessary. It must be continued for years, and be provided less expensively. To furnish this supervision, frequent post-graduate courses for the patient are essential. This policy has been attempted in diabetes camps They are good so far as they go, but they operate for only a month or two in the summertime. We must have islands of safety, hostels, available all the year round and at low costs. Each hospital in the country treating diabetics should have a classroom where a knowledge of diabetes can be taught to patients, their families, out-patients and those living in the immediate neighborhood of the hospital. Such facilities are practicable by the creation of Hospital Teaching Clinics in conjunction with hospitals, to which ambulant patients may go Such patients do not need elaborate nursing care and they can make their own beds and go to the hospital cafeteria. Diet kitchens may advantageously be used without hospitalization. In these clinics, teaching can be intensified but it must be thorough and so good that all will really want to learn. The demonstration of one sore toe, one insulin reaction, one case of coma or of blindness (and do not forget that of the new cases of blindness recently added to the State of Massachusetts list of the blind 18 per cent were diabetics) may prevent a hundred other diabetics from acquiring the same lesions Our own Hospital Teaching Clinic established a year and a half ago, has far exceeded our expectations Never have we had patients so satisfied Never have we had them learn so much in so short a time. Their length of stay is half that of the hospital proper. By no means do we attribute this wholly to our supervision, but rather to the fact that here one patient learns from another patient and this is often of more value than what the doctor says The salvation of diabetics and their relatives should depend

[1] Luntz Brit Med Jour, *1*, 1082 1957

largely on diabetics themselves When a doctor or nurse sits down at a table with a diabetic patient with scales before them and weighs out the

nurses is essential Teach a doctor and the result of it may lead in his lifetime to the treatment of 100 diabetics and the detection and prevention of the disease in a 1000 relatives We need professors, assistant professors and instructors in the treatment of diabetes

are glad to acknowledge that though it is usually not useful for the younger diabetics, and for those requiring more than 20 units of insulin, it is a distinct help for many among the older patients with mild diabetes if they will adhere to their diet We doubt if its evaluation in the treatment of the disease will be known for some years

We still believe the pancreas underlies all diabetes either because of the disease in it or because of its involvement by influences in the pituitary, adrenals, thyroid or liver Even the advent of oral treatment has not changed our conviction

Chapter 2

THE INCIDENCE OF DIABETES

Elliott P. Joslin, M. D. and Leo P. Krall, M. D

A. THE UNIVERSALITY OF DIABETES

Any doubt in my mind about the universality of diabetes was dispelled when I sought and found the reason for the low diabetic death rate of 10 per 100,000 in Arizona, as compared with 42 per 100,000 in Rhode Island for the year 1937. I visited all the communities in Arizona of more than 3,000 inhabitants and interviewed their physicians Age and sex adjustments accounted for a part of the disparity in the death rates. Thus, figures for death [illegible]
100,000.
in the re[illegible]
mortality rate in Rhode Island. The area of Arizona is 113,810 square [illegible]

of physicians per residents in the two states did not differ greatly, their accessibility did, since two-thirds of the population in Arizona lived in communities with populations of less than 2500 In Arizona, Indians comprised 10 per cent and Mexicans 26 per cent of the population, and the Jewish race only about 0 5 per cent.
[illegible]

this nationality was surveyed than any other and, furthermore, doubt still exists as to the actual number of Mexicans in the state. Finally, it is significant that in Arizona, death certificates marked "cause of death unknown" were three and one-half times as numerous as those certificates which ascribed the cause of death to diabetes [illegible]

replied to a questionnaire. The low rate among the Navajo Indians who lead a nomadic life and have a scarcity of food contrasted as expected with the high mortality among the Pimas who were more opulent and hired others to work for them

This diabetic survey in Arizona supports the belief that the incidence of diabetes is highest where (1) the average age is oldest, (2) women predominate; (3) obesity is most frequent; (4) medical supervision is closest; (5) deaths are most accurately reported; and (6) the proportion of Jews is greatest.

B. INCIDENCE AND RECENT CHANGES IN DIABETES MORTALITY

In 1875, Apollinaire Bouchardat,[1] the most famous diabetes clinician of all times writes: "I do not believe I am wrong in saying that among twenty men between the ages of forty and sixty years, belonging to legislative assemblies, to noted learned societies, occupying high positions in commerce

when being examined for life insurance. He found about 1 per cent of the specimens contained over 1 per cent of sugar and twice as many somewhat less His figures represent an understatement because (1) they were based on presumably healthy adults under the age of sixty, whereas (2) 51 4 per cent of diabetic deaths at that time occurred after sixty-five years of age, and (3) they included few females, among whom diabetes is acknowledged to be more frequent after middle life

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the country, or roughly about 3 millions

At the beginning of the century the steady increase in the mortality rate

tuberculosis, and gangrene have almost disappeared from the picture, and

[1] Bouchardat De la Glycosurie ou Diabète Sucré, 1883, Paris, p 180
[2] Barringer Arch Int Med, *3*, 295, 1909
[3] Wilkinson and Krall Jour Am Med Assn, *135*, 209, 1947 (see also page 35)

three-fourths of the patients slip away in old age from the same causes which are common to all mankind.

C THE SIXTH INTERNATIONAL CLASSIFICATION OF CAUSES OF DEATH

A most complicating and confusing factor in studying the incidence or prevalence of diabetes was introduced in 1949, by the Sixth International Classification of causes of death The former practice in this country was to assign the cause of death when diabetes was mentioned on the death

assigns the primary cause. This change in practice has disrupted comparison of recent statistics of mortality from diabetes in the population with those of former years, as well as comparative regional levels of mortality from the disease. It reduced the diabetes death rate nearly one half.

TABLE 1 —NUMBER OF DEATHS FROM ALL CAUSES—DEATHS AND RATES FROM DIABETES AND RATIO OF DEATHS FROM DIABETES TO DEATHS FROM ALL CAUSES REGISTRATION AREA, 1900, 1910, 1920, 1930, 1940, 1945, 1950, 1955, 1956

		Diabetes Deaths				
			Rate per 100,000 Population		*Ratio Diabetes Deaths to Total Deaths (Per Cent)*	
Year	*Total Deaths*	*Number*	*Old Revision*	*Sixth Revision*	*Old Revision*	*Sixth Revision*
1956*	1,565,000	26,340		15 8		1 68
1955	1,528,717	25,488		15 5		1 67
1950†	1,452,454	21,419		16 2		1 68
1950	1,450,270	25,010	29 7	16 6	3 09	1 72
1945	1,401,719	35,160	26 6	15 1	2 51	1 42
1940	1,417,269	35 015	26 6	15 1	2 47	1 41
1930	1,343,356	22,528	19 0		1 67	
1920	1,142,558	14,062	16 0		1 23	
1910	805,412	8,040	14 9		1 00	
1900	539,939	3,996	9 7		0 55	

It is confusing to compare death rates or numbers of diabetics dying recently with those prior to 1949 Studies were made in New York City to show how many diabetics there would be if the Fifth Revision instead of the Sixth Revision were still in use For this purpose, by using the factor 0 57 and applying it to the reported number dying according to the Sixth Revision, one can learn the number by the Fifth Revision. Thus, in 1945 the number of deaths in the country due to diabetes was 35,160 with a rate of 26 6 per 100,000 (See Table 1) In 1950, the number of fatal cases was

reported to be 25,010, rate 16 6 per 100,000, but applying the ratio, the 1950 number would be raised to 44,016 and the rate to 29 7 by the Fifth Revision. [illegible] that more and more one depends upon the

deaths and the death rates have remained practically constant, ranging between 16 6 and 15 5 per cent, as compared to 29.7 per cent by the Fifth Revision

D DEATH CERTIFICATES UNRELIABLE IN ESTIMATING INCIDENCE OF DIABETES

The diabetic deaths recorded even by the Sixth Revision of the Manual of the International Statistical Classification of Diseases, Injuries and *Causes of Death do not represent the total number of persons who die with* diabetes, and for two reasons. The first is the priority accorded by established rules of classification A second factor in the non-recognition of diabetic deaths is the omission of any reference to diabetes by the doctor when reporting the death How frequently this takes place has been variously estimated It occurs (1) because a doctor, new to the patient, may sign the certificate without a knowledge of the existence of diabetes, (2) the

The priority caused by changes in classification differ greatly between the 5th and 6th revisions of the Manual Lombard and Joslin[1] investigated the death certificates of 744 diabetic patients in 1936 and 1000 in 1946, previously treated by Joslin, and found that 63 per cent of the first study and 65 7 per cent of the 2nd study were classified as dying of diabetes, while 13 0 per cent of the 1st study and 9 9 per cent of the 2nd, although dying of diabetes, were otherwise classified and 24 0 per cent of the 1st study and 24 6 per cent of the 2nd failed to have the word "diabetes" on the death certificate

A recent study, 1958, has shown that only 33 per cent of individuals dying with diabetes have been so classified, while 44 2 per cent have been certified

[1] Lombard and Joslin New England Jour Med, *214*, 7, 1936, Am Jour Digest. Dis, *14*, 275, 1947, 1958 study submitted for publication

as dying of other diseases although diabetes is mentioned on the death reacord, and 22.8 per cent failed to have the disease mentioned on the record.

Deaths from cancer, accidents and diseases of the circulatory system constitute the greater number of deaths which have been classified as underlying causes of death

Assuming that what has occurred in Massachusetts, namely that only [illegible] re- [illegible] ility [illegible] ered deaths due to diabetes reported for 1955, in the United States, to approximately 77,000

TABLE 2 —DEATH RATES PER 100,000 FROM DIABETES MELLITUS BY COLOR AND SEX ALL AGES, 1-74 YEARS.

Metropolitan Life Insurance Company, Industrial Department, Weekly Premium Paying Business, 1911-1955

	*Age-Adjusted**					*Crude*				
		White		*Nonwhite*			*White*		*Nonwhite*	
Year	*Total*	*Male*	*Female*	*Male*	*Female*	*Total*	*Male*	*Female*	*Male*	*Female*
1955	8 1	6 4	9 5	7 0	1 2	14 3	8 3	17 6	11 2	22 6
1954	8 6	7 0	9 8	8 8	12 8	14 5	8 7	17 6	13 1	23 5
1953	9 1	7 1	10 9	7 1	12 9	15 3	9 0	19 2	10 8	22 7
1952	8 7	6 6	10 4	6 6	12 7	14 2	8 1	17 9	9 6	22 0
1951	9 2	6 8	11 1	8 0	14 7	14 9	8 3	18 7	11 8	21 6
†1950	9 6	6 9	11 7	8 0	16 5	15 2	8 4	19 1	11 4	27 0
1950	17 0	12 0	21 3	12 3	24 9	31 3	16 6	42 2	17 7	41 4
1945	16 2	10 3	21 6	10 8	23 3	21 8	11 7	34 7	13 6	31 4
1940	22 1	14 0	29 6	13 2	32 1	29 5	13 8	41 1	15 8	44 8
1935	20 5	14 1	26 7	13 2	26 0	24 4	12 6	33 3	14 6	33 6
1930	18 3	13 1	23 3	11 4	21 6	18 4	10 4	21 0	12 0	28 1
1920	15 6	12 7	19 1	9 8	11 7	13 6	9 7	17 4	9 8	12 4
1911	15 1	14 1	17 2	9 7	7 5	13 1	11 2	16 1	8 1	7 8

*Standardized on basis of standard million population of England, Wales, 1901

†Figures below the line 1950-1911 are based on the 5th Revision Classification of deaths, but above 1950 are based on the 6th Revision

It is evident that diabetes morbidity cannot be estimated well from the death records, that long-term trends can be misleading and that a part of the increase in the number of deaths from coronary disease is apparent rather than real

[illegible]

of Deaths Years must intervene before one will be [illegible] conclusions Manifestly, the death rate did not drop from 16 2 per 100,000 in 1945, to 9 6 per 100,000 in 1950 Table 2 discloses the higher death rates

FIG 1 —Diabetes—Crude and adjusted death rates, 1911 to 1950 Metropolitan Life Insurance Company—Industrial Department Based on the Fifth Revision of the International List of Causes of Death

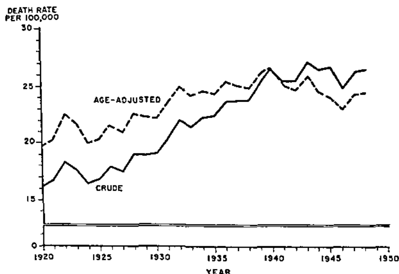


FIG 2 —Crude and age-adjusted death rates from diabetes, United States Registration Area, 1920–1948 Source Public Health Service National Office of Vital Statistics

TABLE 3.—CRUDE AND AGE-ADJUSTED* DEATH RATES FROM DIABETES UNITED STATES, 1949–1956 CLASSIFIED ACCORDING TO SIXTH REVISION

(Excludes Armed Forces Overseas)

Year	Death Rates Per 100,000 Crude	Age-Adjusted
1956†	15 8	13 3
1955	15 5	13 2
1954	15 6	13 3
1953	16 3	14 0
1952	16 4	14 2
1951	16 3	14 2
1950	16 2	14 3
1949	16 9	15 0

*Standardized on the basis of the total population of the United States in 1940

†Provisional

Source National Office of Vital Statistics of the United States Public Health Service, Special Reports-National Summaries

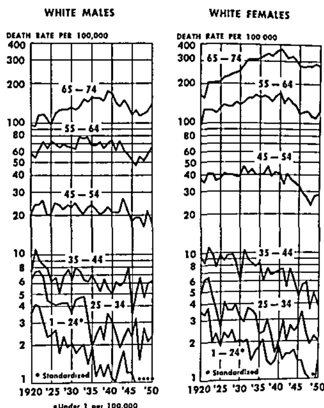


FIG 3.—Diabetes—Death rate by sex and age, 1920–1950 Metropolitan Life Insurance Company, Industrial Department

for females in the Company both for age adjusted and crude rates; though

or age adjusted rates are employed, are brought out in Figures 1 and 2, both for the Metropolitan Life Insurance Company and the United States. This is shown also in Table 3. Without having the crude and age adjusted rates in mind, one would draw quite erroneous conclusions about the trend of diabetes mortality Thus, the trend of diabetes mortality as measured by the crude rate shows an upward trend from 1920 to 1940 The age adjusted

justed rates remained nearly stabilized in the same period

Figure 3 shows even more strikingly the changes which have taken place by sex and age in the Metropolitan The female sex preponderance is definite between the ages of 35 and 44, and is maintained thereafter This discloses the decline in deaths for the ages 1 to 24, 25 to 34, and 35 to 44, for both males and females. Those for the 1 to 24 year period dropped almost to the vanishing point

E THE RELATIVE INCREASE IN DIABETES IN NATION, STATE AND CITY

Any statement about the relative position of diabetes among leading causes of death is subject to individual judgment It depends chiefly upon the plan followed in its compilation If the table is arbitrarily confined to disease, then diabetes advances one place, because accidents exceeded it

TABLE 4 —CHIEF CAUSES OF DEATH IN THE UNITED STATES, 1956 AND 1955
Death Rates Per 100,000 Population

Cause of Death	*1956**	*1955*
All Causes	936 1	930 4
	361 8	355 8
	146 6	146 5
	107 1	106 0
	56 4	56 9
	38 7	39 0
	28 3	27 1
	19 4	19 8
	15 8	15 5
	12 7	12 5
	10 7	10 2

*Data based on a 10 per cent mortality sample
Source National Office of Vital Statistics of the U S Public Health Service

in the term five subdivisions, such as general arteriosclerosis, disease of the heart, vascular lesions of the central nervous system, chronic nephritis and hypertension without mention of the heart," diabetes advances four points more. It would then be exceeded only by (1) malignant neoplasms, (2) vascular disease and (3) influenza and pneumonia. *(See Tables 4 and 5).*

TABLE 5.—DEATH RATES PER 100,000 POLICYHOLDERS FROM SELECTED CAUSES

Metropolitan Life Insurance Company Industrial Premium-Paying Business, 1956

Cause of Death	*Rate*
Disease of the heart	210 9
Malignant neoplasms	128 7
Vascular lesions, central nervous system	63 4
Accidents, total	35 6
Diabetes mellitus	14 9
Pneumonia and influenza	14 0
Cirrhosis of liver	10 6
Nephritis and nephrosis	7 8
Tuberculosis, all forms	7 1

Diabetes has advanced as a cause of death in the United States from 27th in 1900, to 8th place in 1956 if we leave out both accidents and deaths "in early infancy and prematurity." For the Metropolitan Life Insurance Company industrial experience in 1956, it has already passed pneumonia and tuberculosis and ranks sixth as a cause of death or, excluding deaths [illegible]

diabetics

A compilation of 300 cases of diabetes treated at the Bristol Infirmary closely approximates statistics reported thus far.[44]

F VARIATIONS IN DIABETES MORTALITY IN GEOGRAPHICAL AREAS OF THE UNITED STATES

Wide variations occur in diabetes mortality data among the states The average mortality in 1953-55, in the ten Middle Atlantic states was 21 5, (New England 19 7 and East with Central 18 per 100,000) as compared respectively with the three sections Eastern with Central, Mountain, Pacific where it was respectively 10 6—10 6—10 7 per 100,000 (Table 6) [illegible] with the [illegible] ion It is [illegible] is relative [illegible] h for the states with the highest and those with the lowest mortality. To me the

[44]British Med Jour, *1*, 1149, 1958

probabilities are that the same explanation holds for these variations in mortality as appeared to hold for Rhode Island and Arizona.

TABLE 6—AVERAGE ANNUAL DEATH RATES PER 100,000 FROM DIABETES IN THE UNITED STATES

By Geographic Region and State,* 1953–1955

Region and State	*Rate*	*Region and State*	*Rate*
UNITED STATES	15 8	South Atlantic (Continued)	
New England	19 7	Virginia	10 6
Maine	16 9	West Virginia	12 4
New Hampshire	23 2	North Carolina	10 0
Vermont	16 7	South Carolina	11 1
Massachusetts	19 7	Georgia	11 2
Rhode Island	26 9	Florida	12 6
Connecticut	17 9	East South Central	10 6
Middle Atlantic	21 5	Kentucky	12 7
New York	20 5	Tennessee	9 0
New Jersey	21 1	Alabama	9 9
Pennsylvania	23 1	Mississippi	10 9
East North Central	18 8	West South Central	11 5
Ohio	22 5	Arkansas	10 2
Indiana	17 1	Louisiana	14 5
Illinois	15 3	Oklahoma	13 8
Michigan	20 1	Texas	10 2
Wisconsin	18 2	Mountain	10 6
West North Central	16 5	Montana	16 0
Minnesota	17 1	Idaho	12 4
Iowa	16 3	Wyoming	12 4
Missouri	15 8	Colorado	10 3
North Dakota	14 1	New Mexico	6 8
South Dakota	15 5	Arizona	8 1
Nebraska	19 7	Utah	12 1
Kansas	15 8	Nevada	9 4
South Atlantic	12 1	Pacific	10 7
Delaware	20 2	Washington	14 5
Maryland	17 4	Oregon	10 9
District of Columbia	13 2	California	10 0

*By place of residence Excludes Armed Forces overseas

Source National Office of Vital Statistics of the U S Public Health Service Special Reports—National Summaries

G AGE AND CHANGING INCIDENCE OF DIABETES AND DIABETIC MORTALITY

The increase in diabetic mortality is limited to individuals in the older age groups Since the introduction of insulin, deaths from diabetes in individuals under fifty years of age [illegible]

chusetts in Table 7

Three factors have been instrumental in accomplishing this change: (1) the aging of the total population, shown by the average age of the living and the average age at death (Table 8) and the percentage distribution of the total population in the United States (Table 9): (2) the increasing duration of life of the modern diabetics (Tables 36 and 37, p. 225 and 226), (3) the

greater attention to diagnosis of diabetes in young and aged people as shown by decades of onset of diabetes

Between 1900-1914 and 1956-1957, the average duration of life of all the fatal diabetics in our group had increased from 4.9 years to 18.2 years (Table 38, p 228); but from studies of special series of cases, dead and living,

TABLE 7 —PER CENT OF DEATHS FROM DIABETES BY DECADES OF AGE

(Massachusetts, 1901-1932, 1933-1950, 1950-1955)

Per Cent

	1901-1932		1933-1950		1950-1955	
Years	*Males*	*Females*	*Males*	*Females*	*Males*	*Females*
0-9	2.7	1.9	0.4	0.2	0.4	0.3
10-19	4.7	2.9	0.7	0.5	0.2	0.3
20-29	4.7	3.2	1.2	0.7	1.0	0.7
30-39	6.2	4.0	2.3	1.1	3.0	1.4
40-49	9.7	8.0	5.8	3.5	5.9	2.7
50-59	20.0	21.7	16.6	15.1	14.2	11.2
60-69	28.8	32.8	30.7	34.7	29 01	31.1
70-79	18.5	20.3	31.3	32.9	32.2	35.4
80	4.7	5.2	11.0	11.3	14.0	14.9
	100.0	100.0	100.0	100.0	100.0	100.0
Number of Deaths	8,744	13,492	10,794	20,615	2,285	3,998

TABLE 8 —POPULATION, BIRTH RATE, AVERAGE AGE, MEDIAN AGE, AVERAGE AGE AT DEATH, EXPECTATION OF LIFE IN THE UNITED STATES—1860-1956

Year	*Population (thousands)*	*Birth Rate (B R A) per 1,000*	*Average Age Living*	*Median Age Living*	*Average Age at Death*	*Expectation of Life at Birth, Total U S White Male*	*White Female*
1860	31,443		23.3	19.4	22.7		
1870	38,588		24.2	20.1	25.2		
1880	50,156		24.8	20.9	26.9		
1890	62,948		25.8	21.4	31.1		
1900	75,995		26.3	22.9	35.2	48.2†	51.1†
1910	91,972	25.1§	27.2	24.0	38.7	50.2	53.6
1920	105,711	23.7	28.0	25.2	41.9	54.1	56.4
1930	122,775	18.9	29.5	26.4	48.7	59.1	62.6
1940	131,669	17.9	31.6	29.0	55.0	62.9	67.3
1948	146,571*	24.2	31.8	29.8	58.8	65.5	71.0
1949	149,215*	24.0	31.8	29.8	59.2	65.9	71.5
1950	151,132*	23.6	32.1*	30.2*	60.0	66.5	72.2
1955	165,270*	24.6	31.8*	30.0*	61.6	67.3	73.6
1956	168,174*	24.9†	31.7*	29.9*	61.7‡	§	§

*Includes armed forces overseas †Provisional ‡10 Per Cent Sample

§Not available

disease has passed 26 years See Table 39, p 228.

Recognizing the importance of the aging of the population in the frequency of diabetes, the authors have assembled data in Tables 8 and 9, which show how greatly basic data have altered in the United States during the last 90 years Between 1860 and 1956, the population increased from 31,443,000 to 168,174,000 The number of births in 1956, corresponded to a birth rate of 24 9 per 1,000 or over 4,300,000 yearly Expectation of life at birth for white persons, particularly for women, has notably advanced, in 1955 for men to 67 3 and for women to 73 6 years

TABLE 9 — PER CENT DISTRIBUTION OF THE TOTAL POPULATION OF THE UNITED STATES

Including Armed Forces Overseas, 1957 and 1950

Age	*1957*	*1950*
All Ages	100 0	100 0
Under 5	11 2	10 7
5–9	10 5	8 7
10–14	8 8	7 4
15–19	6 9	7 1
20–24	6 3	7 7
25–29	6 7	8 2
30–34	7 2	7 7
35–39	7 0	7 5
40–44	6 6	6 8
45–49	6 2	6 0
50–54	5 4	5 5
55–59	4 7	4 8
60–64	4 0	4 0
65–69	3 2	3 3
70–74	2 5	2 3
75 +	2 9	2 6

Evidently this country is far from having reached its maximum in the percentage of individuals over 60 years of age, despite the rapid strides it has made In 1954, France was said to have the largest proportion of in-

[illegible] These data are available through the

[illegible]

a
1
[illegible] and their ratio
[illegible] In California the
[illegible] to 2 4/5 times

th
of
total number treated which was 640 There remain only 6 of the 640 in

[16]Statistical Bulletin, Metropolitan Life Insurance Company, *39*, 4, 1958

1957. Actually, the average duration of life for 99 per cent of the 640 patients seen in this Naunyn Era was 9.6 years. For details see page 230.

The increasing duration of life of the diabetic and the part it plays in lowering diabetes mortality in the early decades and raising it in the later ones is shown by the average age at death from 326 patients dying in the Naunyn Era, (1897-1914), which was 44.5 years, but for 640 fatal cases in

TABLE 10.—THE AGE AT ONSET OF DIABETES MELLITUS PER CENT OF CASES BY DECADE. BY SEX†

(Experience of Joslin Clinic, 1948-1956)*

Decade	*Male*	*Female*
1	4.5	5.8
2	8.7	7.4
3	6.9	6.4
4	10.9	9.3
5	22.3	19.8
6	25.7	26.6
7	15.6	19.0
8	5.0	5.4
9	.5	.5
10	—	.1
	100.0	100.0
Number of Cases	1699	1783

*Based on a 25% sample of cases—Nos. 26–50

†Prepared by the Statistical Bureau of the Metropolitan Life Insurance Company

TABLE 11.—AGE AT ONSET OF DIABETES. PER CENT OF CASES IN EACH FIVE-YEAR AGE GROUP. BY SEX

(Experience of Joslin Clinic, 1948–1956)*

Age Groups	*Number of Cases*		*Per Cent of Total*	
	Male	*Female*	*Male.*	*Female*
All Ages	1699	1783	100.0	100.0
Under 5	22	28	1.3	1.6
5–9	55	74	3.2	4.2
10–14	86	82	5.1	4.6
15–19	62	50	3.6	2.8
20–24	63	60	3.7	3.4
25–29	54	54	3.2	3.0
30–34	69	74	4.1	4.2
35–39	115	91	6.8	5.1
40–44	168	158	9.9	8.9
45–49	210	194	12.4	10.9
50–54	217	248	12.8	13.9
55–59	219	226	12.9	12.7
60–64	172	210	10.1	11.8
65–69	93	128	5.5	7.2
70–74	61	68	3.6	3.8
75–79	24	28	1.4	1.6
80–84	7	8	.4	.4
85–89	2	1	.1	.1
90–94	—	1	—	.1
Average Age	45.5	46.5		
Median Age	48.7	50.5		

*Based on a 25% sample of cases—Nos. 26–50

†Prepared by the Statistical Bureau of the Metropolitan Life Insurance Company

the Charles H Best Era, (January 1, 1956 to December 11, 1957), when it was 64 7 years (Table 38) More than one-half (53 6 per cent) of our [illegible] (Table 16).

[illegible], 10 and 11, show [illegible]ach decade, at *age* [illegible] Tables 12 and 13 which give the per cent for *age at death* of diabetics based on death rates by five- and ten-year periods for the United States, (Table 12), the Metro-

TABLE 12 —DEATH RATES PER 100,000 FROM DIABETES BY COLOR, SEX AND AGE PERIODS UNITED STATES, 1953–1955

(Excludes Armed Forces Overseas)

	White		*Nonwhite*	
Age Periods	*Males*	*Females*	*Males*	*Females*
All Ages				
Crude	12 8	19 1	9 8	18 7
Age-adjusted*	11 1	14 9	11 7	22 9
Under 1	5	4	1 1	1 1
1–4	3	3	4	1
5–9	3	3	3	3
10–14	4	6	9	8
15–19	5	9	1 4	1 8
20–24	1 5	1 2	1 4	1 5
25–29	2 3	1 6	2 9	2 6
30–34	2 8	2 1	4 0	3 7
35–39	3 6	2 1	5 9	7 6
40–44	4 7	3 1	8 4	14 4
45–49	7 0	6 0	10 2	29 6
50–54	12 2	13 2	21 8	55 4
55–59	21 8	30 5	29 3	70 7
60–64	38 3	61 3	48 6	98 1
65–69	60 6	102 9	62 0	129 3
70–74	91 2	133 5	71 5	135 4
75–79	128 3	173 5	83 6	115 2
80–84	158 0	197 6	89 4	109 4
85–+	150 7	169 1	64 0	89 3

*Based on the total population of the United States, April 1, 1940

Source United States Department of Health, Education and Welfare, Public Health Service, National Office of Vital Statistics, Special Reports, National Summaries, 1953, 1954 and 1955

politan Life Insurance Company (Table 13), and finally, the ratio per age of diabetics found in the National Health Survey in 1935 and 1936, (Table 14) These Tables are not directly comparable, because some are based on the *number alive in different decades, like those in our own special group,* and the others simply represent the number of individuals dying in those decades The onset rates on the other hand are an attempt to represent the susceptibility to the development of diabetes in certain decades for our own series They are of increasing importance in our search for methods to prevent and postpone the onset of the disease Onset data require careful questioning and zeal on the part of the doctor to elicit the truth Evidence

must be sought from changes in weight, appearance of symptoms and previous analyses of urine. Even with the greatest care one often is left in doubt and feels obliged to make data of onset and diagnosis coincide. The mortality rates represent the susceptibility to dying from diabetes in Massachusetts, the United States and in the Insurance Groups. Most of the deaths so reported occur between sixty and eighty years, or twenty years

TABLE 13.—DEATH RATES PER 100,000 FROM DIABETES BY COLOR, SEX AND AGE PERIODS (METROPOLITAN LIFE INSURANCE COMPANY INDUSTRIAL PREMIUM-PAYING BUSINESS, 1953-1956.)

Age Period	White		Nonwhite	
	Males	Females	Males	Females
Ages 1–74				
Crude	8.8	18.1	11.7	22.9
Age Adjusted*	6.8	10.1	7.6	12.6
1–4	.4	.7	—	—
5–9	.3	.3	—	—
10–14	.3	.5	—	—
15–19	.4	1.0	.9	.4
20–24	.7	1.1	1.3	1.9
25–34	1.9	1.7	3.6	2.4
35–44	4.9	2.3	7.6	6.6
45–54	11.3	10.8	14.4	29.9
55–64	31.9	55.3	36.5	65.1
65–74	75.5	136.1	64.5	123.9

*Standardized on basis of standard million population of England and Wales, 1901.

TABLE 14.—RATIO OF DIABETES IN THE POPULATION

Age	Ratio		Diabetics per 1000 Population		
	Males	Females	Total	Males	Females
0–14	1:2500	1:2500	0.38	0.35	0.41
15–24	1:1700	1:1700	0.59	0.62	0.57
25–34	1:1100	1:900	1.00	0.90	1.08
35–44	1:500	1:300	2.61	2.01	3.16
45–54	1:225	1:125	6.56	4.49	8.64
55–64	1:100	1:50	14.25	9.96	18.20
65 and over	1:70	1:45	18.39	14.58	21.47
All ages			3.67	2.73	4.53

The above data are based upon 9182 diabetics in a surveyed (urban) population of 2,502,391 persons. National Health Survey, 1935–1936.

The proportions of the population reported to be diabetic by age and sex, based on the National Health Survey of 2,500,000 persons, are shown in

Table 14 A similar survey is in progress but on a larger scale and should be of great value.

Sex and Diabetes Mellitus.—Sex likewise plays a more and more prominent part in diabetic incidence and mortality, and this is also attributable to two causes The first of these is the growing respect in which

(Table 11) or above the age of seventy years The distinguishing feature

investigators that the average age at menopause occurs more often in the

of the cases reporting cessation of menses at the time of the completion of the insurance medical record give ages between forty-five and fifty as the onset of menopause, which is a year before the median age at which diabetes develops in females Roughly, one-quarter of the cases occur before age forty-five and the remaining quarter after fifty, some cases being reported as late as age sixty

In Massachusetts for 1950-1955, the number of deaths ascribed to diabetes among males was 2285 or 36 per cent, and for females, 3998 or 64 per cent (Table 7), In the United States the definite excess of deaths of females over

about 70 pe

from forty-

betes morta

Of the coun

exceptions to the rule In those two countries the rates for males are slightly, but not significantly, higher than for females

The death rates for diabetics are considerably higher for whites than non-whites in the United States for 1953 to 1955 The difference is insignificant up to age of 25, but from here on to age 70 there is a higher per-

the higher death rate of non-whites in middle life (Table 12)

The death rates are greater for males and females in the colored race between the ages of 25-65 years as compared with whites in the same age bracket in both the United States Vital Statistics and the Metropolitan

[a] Joslin Treatment of Diabetes Mellitus, 7th ed, Philadelphia, Lea and Febiger, p 34, 1940

Life Insurance Company series. However, for white males the death rate is higher above the age of 65 years and for white females above the age of 75 years, in the United States Vital Statistics series, and above 65 years for each sex in the Metropolitan Life Insurance Company series

Marital Condition in Relation to Diabetes.—The incidence of diabetes is higher in married women than in single women. This difference is not

confirmed by similar Canadian data in the period from 1928 to 1932

made for age

TABLE 15.—AGE-ADJUSTED* DEATH RATES PER 100,000 FROM DIABETES BY SEX AND MARITAL STATUS, WHITE PERSONS, AGES 20–74 (UNITED STATES, 1949–1951)

Marital Status	*Males*	*Females*
Single	18 2	12 6
Married	13 4	22 4
Widowed	19 6	25 3
Divorced	22 8	21 2

*Adjusted on the basis of the age distribution of the total population residing in the United States on April 1, 1950

Source Metropolitan Life Insurance Company, Statistical Bulletin, vol 38, p 5, February 1957

Living Diabetics—Experience of Joslin Clinic.—The percentage dis-

, and for females 50 5 years—also a

Apparently male humans, like

ales living invariably ex-

nated number of our dia-

2, was 15,000

[6] Mosenthal and Bolduan Am Jour Med Sci, *186*, 605, 1933

TABLE 16 —AGE DISTRIBUTION OF LIVING DIABETICS, NUMBER AND PER CENT OF CASES IN EACH AGE GROUP BY SEX

(Experience of Joslin Clinic, 1898–1952)*

Age Groups	*Number of Cases* *Total*	*Male*	*Female*	*Per Cent of Total* *Total*	*Male*	*Female*
All Ages	4867	2275	2592	100 0	100 0	100 0
Under 5	10	6	4	2	3	2
5–9	35	19	16	7	8	6
10–14	89	38	51	1 8	1 7	2 0
15–19	139	70	69	2 9	3 1	2 7
20–24	189	82	107	3 9	3 6	4 1
25–29	252	114	138	5 2	5 0	5 3
30–34	225	105	120	4 6	4 6	4 6
35–39	228	120	108	4 7	5 3	4 2
40–44	284	163	121	5 8	7 2	4 7
45–49	358	207	151	7 4	9 1	5 8
50–54	446	219	227	9 2	9 6	8 8
55–59	617	336	281	12 7	14 8	10 8
60–64	708	314	394	14 5	13 8	15 2
65–69	565	229	336	11 6	10 1	13 0
70–74	376	122	254	7 7	5 4	9 8
75–79	216	80	136	4 4	3 5	5 2
80–84	98	39	59	2 0	1 7	2 3
85–89	26	11	15	5	5	6
90–94	5	1	4	1	—	2
95–99	1	—	1	1	—	—
Med age	56 4	54 9	58 3			

*Based on a 25 per cent sample of cases—Nos 26–50 Living to January 1, 1953
Prepared by the Statistical Bureau of the Metropolitan Life Insurance Company

H THE DIABETES PROGRAM OF THE U S PUBLIC HEALTH SERVICE

The Oxford Study.—When Wilkerson and Krall of the U S Public Health Ser[illegible]

had been made but the Oxford study was unique because it combined a history with postprandial blood and urine sugar values in addition to glucose tolerance tests This method uncovered a total of 70 cases which included 40 previously known and 30 newly discovered diabetics and indicated a prevalence of 2 0 per cent of those tested, or a projected 1 7 per cent of the entire population of the town This was much higher than hitherto published estimates and was the basis for the often-cited "million unknown diabetics" figure which is probably far too conservative Oxford, Massachusetts, is also unique in that each age group corresponded within 1 per cent to the average number of persons in each age group in the United States as a whole

Four years later, the authors returned for a progress study[8] to determine the status of those 70 originally classified as diabetics, the 118 with higher

[6] National Health Survey, 1935-1936, Bulletin 6, Sickness and Medical Care Series, U S P H S, 1938
[7] Marks New England Jour Med, *235*, 289, 1947
[8] Wilkerson and Krall Jour Am Med Assn, *152*, 1322, 1953

than normal blood sugar levels (above 140 and below 170 mg. per cent postprandial Folin-Wu) and the 17 found to have repeated glycosuria. In addition, a control group of 225 were selected to match the above groups on the basis of age and sex distribution. This latter group was found to be "normal" in the original study. In the intervening four years, 16 of the original 70 diabetics died. Investigation of the remainder of the study group suggested that the original figures were probably conservative because while only 4 new diabetics (1.8 per cent) were found in the "control" or normal group, a total of 17 (14.4 per cent) were diagnosed in the blood sugar suspect group. In other words, those with slightly elevated blood

the gap between detection, onset and progression of complications as well as for a point of comparison for future long-term epidemiological studies. This report, which included history, physical examination by an internist

eyes, heart and great vessels. By frequent serial studies of this type, the inception and the detectable onset of complications can be pinpointed within 6-month periods. Since many varying degrees of control exist in these patients, the information obtained in this study may be useful in demonstrating whether early detection and adequate treatment can prevent or forestall complications.

Now, more than 10 years after the original report, it is interesting to note the fate of the original 70 cases.[10] Of the 40 "previously known" diabetics, two are not available, 19 are alive and presumably still diabetic while 19 others have died (11 cardiovascular, 3 cerebrovascular, 2 renal, 2 carcinoma, 1

[9] Wilkerson and Krall. Loc. cit., p. 35.
[10] Wilkerson, Krall and Butler. Diabetes in a New England Town. (Interim Report after 7 years.) Awaiting publication.

With this continuing serial study, much more valuable information will be available in the future.

I DETECTION OF DIABETES

LEO P. KRALL, M. D.

Of all the chronic diseases, diabetes is the one condition which can be readily detected and confirmed That there remain more than one million undetected diabetics indicates that current known techniques have not been

be reproduced by an average technician and (3) the validity of the test, which indicates the frequency of test confirmation by accepted diagnostic methods [16] These methods of detection[17] include urine tests and blood

Wilkerson-Heftmann methods The urine sugar tests can be analyzed by technicians trained in the necessary techniques or by individual, self-testing devices with results then reported to the individuals' private physicians. The blood sugars may be analyzed by (1) individually trained technicians, (2) Hewson Clinitron, a 50-pound machine used to check blood sugar values at a pre-set screening level,[18] (3) the Technicon Autoanalyzer (Technicon Co Chauncy N Y), a relatively expensive but ingenious device which reportedly does blood sugar determinations on a 0.3 cc blood specimen in one and one-half minutes, or a total of 40 to 60 determinations per hour,

cation of the American Diabetes

Role Ibid, 1957
6

cation and Welfare, Washington

[16] Diabetes Program Guide Loc cit p. 37.
[17] Ibid Loc cit p 37
[18] Ibid Loc cit p 37.

All screening tests are faced with the problem of sensitivity versus specificity. Sensitivity is the percentage of true diabetics rated as positive by a given test. Specificity, on the other hand, is the percentage of true non-

ensitivity increases as spe-
ntly, a high screening level
a few false positives, while

a low screening level will show many false positives but will also find a greater number of early and incipient diabetics. Therefore, any screening level must be a compromise between the ideal and the practical. Earlier surveys[19,20] and more recent studies[21] have indicated that the post-prandial blood sugar value is more efficient than urine sugar tests as a case finding device. This increased accuracy is accompanied by a higher cost per test and the relative inaccessibility of blood for testing. The ultimate choice of test must consider all factors. Obviously a screening technique utilizing both blood and urine tests is ideal, although not always feasible.

There has been much debate about the relative merits of the Folin-Wu blood sugar test as compared with the Somogyi-Nelson and Wilkerson-Heftmann methods. The Folin-Wu test[22] is most widely used but measures other reducing substances in addition to glucose and consequently gives higher blood sugar values. The Somogyi-Nelson[23,24] test measures only the true glucose present. This is slower and considered somewhat involved for widespread screening. The Wilkerson-Heftmann[25] test can be read only above or below a pre-set screening level and requires the mechanical Clinitron. Actually, the differences are more apparent than real and successful case finding can be accomplished by any of the screening methods if they are adapted to the needs of the program and if it is borne in mind that "it is not advisable to interpolate from one test to the other but that each should have its own criteria for interpretation."[26]

Diabetes Surveys.—Mass screening techniques have been carried out on a large scale since 1947. *Since that time a total of 109 surveys*[27] *have* tested some 1,067,637 persons in the United States and Canada. About 75 per cent of these projects used blood tests alone or in combination with urine tests. The most commonly used screening level was 130 mg. per 100 cc. of venous blood without regard to prior food intake. The doubtful cases were usually referred to their own physicians who made the final diagnosis. The average study result appeared to vary from 1.0 to 1.5 per cent ... thor-
ough ... ation
The ... ers of

cent among the 156 Indians over the age of 14, who were tested in Ignacio, Colorado

Surveys in Foreign Countries.—In West Cornwall, England, a survey of diabetics was completed by Andrews[28] This is an isolated geographical area with a population of 266,389, of whom 104,827 or 39 9 per cent were surveyed The work was done by Dr Andrews with the help of some 50 general practitioners They found 593 diabetics and of these 579 were confirmed, which gave a rate of 5 6 per 1000 and is considered high in comparison with previously published figures for England as a whole. Among the diabetics there were 3 females for each 2 males, with a tendency for males to predominate up to age 40, but with a striking excess of females in the sixth and seventh decades and a tendency for male predominance

in 1954, and 4 1 in 1955 The female patient tended to have rather more illness than the male Diabetes and its complications were responsible for 15 5 per cent and 13 8 per cent respectively, of all the days spent in bed for the two years investigated It was estimated that the general practitioner

ss in a year and is consulted by

Of all admissions to the hospital,

It is suggested that one medical

bed for every 100 of the diabetic population is required in this area Cardiovascular disease was the cause of death in more than half of the patients followed up The age at death for both sexes was 67 1 years

Professor Ekrem Serif Egeli of the 3rd Medical Clinic of the University of Istanbul, Turkey, reports that 3 9 per cent of the 23,665 patients admitted to the Clinic between 1943 and 1957, had diabetes There were 50 deaths, 5 5 per cent and of these 7, or 14 per cent were due to diabetic coma Of the 32 autopsied cases arteriosclerosis was noted in 6, arteriolosclerosis in 9, pyelonephritis in 7, abscess of the kidney in 2, papillary necrosis in 1, intercapillary glomerulosclerosis in 6 and acute renal failure in 1

Heredity was reported as familial in 58, 6 3 per cent, and hereditary in 107 cases, 11 7 per cent

population Males 456,

showed the greatest num

but 1 case in the first decade, but there were 4 in the ninth

Professor Sedat Tavat states that the incidence of diabetes at the Tedavi Klinigi was 0 62 per cent—432 diabetics among 72,978 admissions, 1952–1957 In Professor Tavat's 75-bed section of the University Clinic the per cent of diabetics was 6 15 per cent Since September 1957, until the end of the year, in a special section of the out-patient department dealing with diabetes the proportion of diabetics reached 6 43 per cent Heredity, 22 4 per cent

Dr Zeytinoglu says intermarriage between cousins is common among the village people, who constitute 71 per cent of the total population in

[28] Andrews Brit Med Jour, 1, 427, 1957

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a low screening level will show many false positives but will also find a greater number of early and incipient diabetics. Therefore, any screening level must be a compromise between the ideal and the practical. Earlier surveys[19, 20] and more recent studies[21] have indicated that the post-prandial blood sugar value is more efficient than urine sugar tests as a case finding device. This increased accuracy is accompanied by a higher cost per test and the relative inaccessibility of blood for testing The ultimate choice of test must consider all factors. Obviously a screening technique utilizing both blood and urine tests is ideal, although not always feasible.

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Diabetes Surveys.—Mass screening techniques have been carried out on a large scale since 1947 Since that time a total of 109 surveys[27] have tested some 1,067,637 persons in the United States and Canada About 75 per cent of these projects used blood tests alone or in combination with urine tests The most commonly used screening level was 130 mg per 100 cc of venous blood without regard to prior food intake The doubtful cases were usually referred to their own physicians who made the final diagnosis The average study result appeared to vary from 1 0 to 1 5 per cent diagnosed as diabetic, depending on the type of population, the thoroughness of the testing technique and effectiveness of the organization The smallest yield was 0 1 per cent among 3,547 industrial workers of Peabody, Massachusetts, while the largest percentage found was 8 3 per

Cambridge, England, in July, 1955. The Third Congress convened July 21–25, 1958, at Dusseldorf, West Germany.

Joslin by the Rector of the Medical Academy of Dusseldorf. Professor

persons so far as their health permits and should assume their full place in society, particularly in its working quota. He has helped provide jobs on his farm, in his laboratory and even in neighboring factories, enabling them to be partly self-supporting. Many simultaneous meetings and panels took place. The main topics covered were: Mechanism of the Action of Insulin, Relationship between Carbohydrate and Fat Metabolism, Carbohydrate Metabolism, Angiopathy in Diabetes; Methods of Blood Determination of Insulin, Insulin Antibodies and Inhibitors, Oral Treatment; Diabetes in Pregnancy, The Diabetic Child, Diabetes Detection Drives, Driving Licences. The Lay Section discussed the problems of social security including employment, taxes and insurance, nutrition and diet,

Joslin and R. Levine of the United States, Dr. J. P. Hoet of Belgium, Dr. W. J. H. Butterfield of Great Britain, Prof. A. L. Loubatières of France and Drs. G. Katsch and K. Oberdisse of Germany.

K RACE AND DIABETES

In general the diabetic studies of Cohen[33] among the Indians of the American Southwest have confirmed the results found by Joslin in Arizona (See page 18). The prevalence of diabetes was determined among 16,296 consecutive admissions over a 2 year period to hospital facilities of the

and diabetes was infrequent in admissions to hospitals on their reservations. The Apache reservation is geographically adjacent to that of the Navajos, a group previously remarked for their low prevalence of this disease. The freedom from diabetes of the Papago Indian, who shares a common environment with the tribes having the highest prevalence, is a subject for speculation, but

group

[33] Cohen. Ann. Int. Med., *40*, 588, 1954.
[34] Rabinowitch. Canadian Med. Assn. Jour., *34*, 487, 1936.

Turkey. Therefore, it will be of great interest to learn whether, because of this, the percentage of heredity in Turkey is particularly high.[28a]

Turkey has made such strides in the treatment of malaria, trachoma and tuberculosis that one can look forward to advances in the detection and treatment of diabetes in the near future. Evidently in the large hospitals the care of the diabetic resembles that in similar institutions in the United States. During the past 8 years 23,730 new hospital beds have been provided, bringing the total for the country up to 31,396. In 1949 there were 16 health centers, and now, 1958 there are 216.

Dr. Joan Wall [illegible]

may be due to the fact that the English group screened with urinalysis one-half hour after a lunch plus 20 grams of glucose, while the Oxford study did blood sugar determinations one hour after a large meal. Consequently, the present 1.13 per cent may be conservative

The College of General Practitioners is undertaking a large scale diabetes survey[30] in Great Britain by checking at least 50,000 persons with a two-hour post-prandial urine glucose test.

Dr. N. Nakayana[31] in summarizing diabetes detection drives in Japan estimates a diabetes prevalence of 3 5 per cent in people over the age of 40

There is much honest difference of opinion among many physicians regarding the cost and effectiveness of large scale screening surveys. One alternative appears to be more education at the professional and lay level with emphasis on case finding by individual physicians, industrial groups or in connection with other screening methods, using some of the newer multiple screening techniques.[32] Certainly, the most fruitful areas for case finding are among the older age groups, the overweight and those with diabetic relatives

In the last analysis, large scale case finding programs must be related to the needs and desires of the community, the available resources and the degree of cooperation between the participants at every level in the community

J INTERNATIONAL DIABETES FEDERATION

The world-wide recognition of the increasing importance of the detection and treatment of diabetes and its complications led to the formation of the International Diabetes Federation with the purpose of the exchange of new ideas, new discoveries and a wider dissemination of knowledge about diabetes The First International Congress, held under the auspices of the [illegible]

Mexico	1955	5	407,522	1,571	5 3
Netherlands	1956	5	84,521	1,377	12 6
New Zealand (incl Maori)	1955	1	17,953	205	10 2
Northern Ireland	1956	-0	14,858	89	6 2
Norway	1955	2	29,099	226	6 6
Panama	1955	·0	8,042	51	5 9
Portugal (incl Islands)	1956	0	106,919	588	6.7
Puerto Rico	1955	-0	16,221	141	6 2
Scotland	1956	8	61,792	473	9 2
Spain	1953	8	273,571	1,825	6 4
Sweden	1955	8	68,634	721	9 9
Switzerland	1955	9	50,366	694	13 9
U of South Africa, European	1954	-0	24,106	264	9 4
United States	1955	·0	1,528,717	25,458	15 5
Ceylon	1956	-0	87 561	585	6.7
West-Berlin	1956	7	32,207	136	6 1
Germany, Federal Rep	1955	0	541,324	5,251	10 5
Mauritius	1955	4	7,088	37	6 7
Paraguay	1955	-0	7,331	30	1.9
Trinidad & Tobago	1956	·0	7,136	126	17 0
Venezuela	1955	3	58,959	260	4 5
Taiwan (Formosa)	1955	7	76,585	142	1 6
Hongkong	1955	-0	19,080	24	1.0
Singapore, Island	1955	4	10,573	73	6 0
Germany, Democratic Rep	1955	·0	214,066	1,841	10 3
Saarland	1955	1	10,022	158	15 9
Malta & Gozo	1955	9	2,683	82	26 1
Yugoslavia[1]	1955	·0	44,136	263	5 2

[1]Yugoslavia *Data refers to only 28 7 per cent of the whole population of the country* (Total population in 1955. 17,636,000)

TABLE 17.—POPULATION. DEATHS ALL CAUSES. DEATHS FROM DIABETES MELLITUS. DEATH RATES PER 100,000. (Prepared by World Health Organization, Geneva)

Country	Year	Population	Deaths All Causes	Deaths from Diabetes Mellitus: Actual Numbers	Deaths from Diabetes Mellitus: Rate per 100,000
Australia	1956	9,427,600	86,088	1,212	12.9
Austria	1956	6,983,900	86,824	650	9.3
Belgium	1955	8,868,475	108,743	2,118	23.9
Canada (whole country)	1956	16,080,791	131,961	1,820	11.3
Chile	1954	6,597,028	84,579	425	6.4
Colombia	1956	12,939,140	171,984	425	3.3
Costa Rica	1956	1,014,170	9,518	69	6.8
Denmark	1956	4,466,400	39,558	312	7.0
Dominican Rep	1954	2,438,000	20,599	42	1.7
Egypt, localities H. B.	1954	9,369,000	200,318	514	5.5
El Salvador	1954	2,121,869	31,810	63	2.0
England & Wales	1956	44,667,000	521,331	3,242	7.3
Finland	1956	4,290,500	38,713	257	6.0
France	1956	43,647,649	541,891	5,557	12.7
Guatemala	1955	3,258,083	67,088	62	1.9
Hawaii	1955	560,000	3,213	102	18.2
Hungary	1956	9,832,601	101,236	659	6.7
Iceland	1956	161,000	1,152	3	1.9
Ireland (Irish Free State)	1956	2,898,000	33,910	207	7.1
Israel (Jewish pop.)	1956	1,628,986	10,276	60	3.7
Italy	1955	48,015,500	446,639	5,335	11.1
Japan	1956	90,253,000	724,028	2,553	2.8

Mexico	1955		5	407,522	1,571	5 3
Netherlands	1956		5	84,521	1,377	12 6
New Zealand (incl Maori)	1955		1	17,953	205	10 2
Northern Ireland	1956		0	14,858	89	6 2
Norway	1955		.2	29,099	226	6 6
Panama	1955		0	8,042	51	5 9
Portugal (incl Islands)	1956		·0	106,919	588	6 7
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United States	1955	1	0	1,528,717	25,488	15 5
Ceylon	1956		0	87,561	585	6 7
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Germany, Federal Rep	1955		0	541,324	5,251	10 5
Mauritius	1955		·4	7,088	37	6 7
Paraguay	1955		·0	7,331	30	1 9
Trinidad & Tobago	1956		0	7,136	126	17 0
Venezuela	1955		3	58,959	260	4 5
Taiwan (Formosa)	1955		7	70,585	142	1 6
Hongkong	1955		-0	19,080	24	1 0
Singapore, Island	1955		.4	10,573	73	6 0
Germany, Democratic Rep	1955		0	214,066	1,841	10 3
Saarland	1955		1	10,022	158	15 9
Malta & Gozo	1955		9	2,683	82	26 1
Yugoslavia[1]	1955		·0	44,136	263	5 2

[1]Yugoslavia Data refers to only 28 7 per cent of the whole population of the country (Total population in 1955 17,636,000)

pretend to make a real search for such but he found no clinical evidence of diabetes among them. Of all the urines of Eskimos which he examined, there were only three which contained a reducing substance but this later was found to be non-fermentable. At that time he estimated the diet as carbohydrate 30–40, protein 250–300, fat 150 grams.

E. M. Scott and I. V. Griffith[35] investigated this question. Blood sugars were done of 869 Eskimo men between 17 and 50 years and 358 men and women over 35 years of age. Three confirmed and 2 possible cases were found. The three confirmed cases were all from the Nome area. He agreed to the general supposition that diabetes was rare among Alaskan Eskimos. One reason for the paucity of diabetes would be that the median age for Eskimos in 1950, was 17.7 years and only 23 per cent of a group of Eskimos were over 35 years of age.

Mrs. Ralph S. Mills, former President of the Ontario Division of the Canadian Diabetic Association has taken great interest in the possibility of diabetes among Eskimos. She has sought information by letter, travel and [illegible]

from the Nome area. The whole question is still in abeyance and there well may be more cases but whether many, or any, of these cases were absolutely pure blood Eskimos is a question.

L. THE WORLD HEALTH ORGANIZATION

I am deeply indebted to the World Health Organization and to Dr. Yves Biraud, Director of the Division of Epidemiological and Health Statistical Services, for Table 17. This gives the most complete data of which I am aware for the estimated population, deaths from all causes and deaths from diabetes and rate per 100,000 in 50 different countries for the year opposite the name of each country.

Of the 13 countries with 100 or more diabetic deaths, Belgium is the highest with 2118 deaths and a rate of 23.9, and Japan the lowest with 1553 and a rate of 2.8. Next to Belgium comes the United States with 25,433 and a rate of 15.5. Obviously, differences in the methods of recording deaths must account in large measure for the death rates of countries neighboring to Belgium, namely the Netherlands 12.6, Denmark with only 312 deaths and a rate of 7, Finland 257 deaths and a rate of 6. France showed a rate of 12.7 compared with 11.2 for 1948, and Sweden 9.9 com- [illegible]

with 8.4 in 1950, and that Australia shows a drop from 18.6 in 1949, to 12.9 in 1956. Belgium in 1949, had a rate of 17.7 but in 1955, it was 23.9. What can be the reason for it?

In a way it is encouraging to have the death rates go up because it would suggest more accurate diagnoses. The low rates in Central and South

[35] Scott and Griffith: Metabolism, 6, 320, 1957.

TABLE 18.—POPULATION, DEATHS ALL CAUSES, DEATHS FROM DIABETES MELLITUS AND DEATH RATES PER 100,000

City	*Year*	*Population*	*Deaths All Causes*	*Deaths from Diabetes Mellitus* — *Actual Number*	*Rate per 100,000*
Montreal	1950	1,232,310	9,802	176	14.3
Tokyo	1954	6,625,000	38,752	82	1.2
Auckland, excl Maoris	1954	401,570	3,565	47	11.7
Wellington, excl Maoris	1954	227,590	1,407	16	7.0
London*	1956	3,273,000	38,317	242	7.4
West Berlin	1956	2,221,507	32,207	136	6.1
Brussels	1955	981 636	16,881	276	28.1
Copenhagen	1956	750,000	7,717	61	8.1
Paris	1955	2,900,000	29,545	328	11.3
Rome	1955	1,822,000	14,584	238	13.1
Havana	1950	734,000	8,159	89	12.1
Rio de Janeiro	1955	2,750,000	31,845	184	6.7
Montevideo	1956	903,200	10,457	74	8.2
Bogota	1955	806,640	9,515	51	6.3

* Administrative County

TABLE 19.—DEATH RATES PER 100,000 FROM DIABETES MELLITUS IN THE 12 LARGEST CITIES IN THE UNITED STATES IN 1955

City	*Population 1955*	*Deaths* 1953	*1954*	*1955*	*Death Rates 1955*
Cleveland	933,700	271	284	313	33.5
Boston	713,200	172	140	206	28.9
Baltimore	968,600	204	190	222	22.9
Philadelphia	2,147,200	601	544	483	22.5
Detroit	1,893,700	374	408	412	21.8
New York	7,822,700	1,711	1,640	1,676	21.4
St Louis	844,200	170	168	162	19.2
Milwaukee	694,100	127	123	111	16,0
Washington, D C	821,100	115	119	115	14.0
Chicago	3,728,100	532	534	491	13.2
Los Angeles	2,235,000	246	236	294	13.2
San Francisco	776,000	90	89	100	12.9

Sources (a) Mid-year 1955 population figures are estimated from special censuses and estimates by the Bureau of the Census and by state and local agencies *Statistical Bulletin*, Metropolitan Life Insurance Company, February 1958, p 5
(b) Deaths—Annual volume of vital statistics of the United States

What a subject for study is Malta with a rate of 26.1! What is the real explanation of that?

In ten years the population of Israel has trebled and medical facilities have similarly increased Soon it will be possible to know whether diabetes is more common in Jews, especially if obesity can be excluded

To the World Health Organization in Geneva, I am indebted also for Table 18, which gives information about 14 cities in various parts of the world concerning population, deaths from all causes, deaths from diabetes mellitus and death rates per 100,000. Brussels has nearly twice the diabetic deaths of any of these 14 cities and is surpassed only by two, Cleveland and Boston, of the 12 American cities listed in Table 19. Tables 17 and 18 and 19, will be increasingly valuable for comparison as new data are acquired in the next few years.

Chapter 3

THE ETIOLOGY AND PREVENTION OF DIABETES[1]

PRISCILLA WHITE, M.D. and ELLIOTT P. JOSLIN, M.D.

HEREDITY is the basis of diabetes. Heredity was noted in the seventh century A.D. in India in thin persons with severe diabetes, according to Ponteva,[2] and Rathery[3] states that Rondelet, a doctor of Montpellier, at the beginning of the sixteenth century suggested its etiological bearing. Morton[4] described it in 1696, and it was considered paramount by Naunyn, although the short duration of the diabetic life in his day and the somewhat less general examination of the urine allowed him to recognize heredity in only 18 per cent of his patients. For years the authors have taken a lively interest in securing information upon heredity from their clientèle and for years have requestioned their patients at their subsequent visits. The term *heredity* is divided into *hereditary* and *familial*. Under *hereditary* are included grandparents, parents, uncles, aunts and children, under the term *familial*, brothers, sisters and cousins. The total incidence of diabetes in families of 6357 of our patients seen between 1897 and 1928 studied by the Metropolitan Life Insurance Company was 24.5 per cent. It appears that in 15.9 per cent it was hereditary, 8.6 per cent familial and 3.3 per cent both. The incidence of heredity among our 1619 cases treated at the New England Deaconess Hospital during 1941 was 41 per cent and for those with onset under fifteen years was 49 per cent. In the oldest age group, seventy-five years of age or over, it was 29 per cent. In fact, that is the lowest percentage of diabetic heredity of any age group in the 1941 series. Among 4054 children in 1957, the heredity was 41.6 per cent and for 1072 cases with onset in childhood, but of 20 or more years' duration, the heredity was 57 per cent. For 106 cases with presumable duration of 40 or more years the heredity was at least 52 per cent and for our Quarter Century Victory Medal cases 65 per cent. In this year 1958, it is seldom one secures a record of diabetes in 4 generations and most exceptional for its presence in 5 generations. For the children of Jewish parentage the heredity was 49 per cent. At the Elliott P. Joslin Camp for boys in 1950 the known heredity for 135 boys was 56 per cent.

[1] [illegible]

[2] [illegible]

[3] Rathery: Le Diabète Sucré, Leçons Cliniques, J. B. Baillière et Fils, p. 7, 1938.

[4] Cited by Allen, Stillman and Fitz: Total Dietary Regulation in the Treatment of Diabetes, New York, Rockefeller Inst. for Med. Res., p. 9, 1919.

Blotner and Hyde[5] studied the family history of 126 cases of diabetes and 77 of glycosuria discovered in their survey of 45,650 selectees at the Boston Induction Station and found it to be 32 per cent for the diabetics and 9

to 5 2 per cent among a control

a subsequent survey of 1383 cases

by Blotner,[6] there was a family

13.7 per cent for the 329 cases who knew they had diabetes. The incidence of diabetes in the families of diabetics as contrasted with the general population was well shown in the study of relatives and non-relatives of the diabetics in Florida. There it was found that it was 5 times as common, 4.2 per cent versus 0 9 per cent, among the relatives as non-relatives.

per cent and among the N

reports that 16 9 per cent

heredity in contrast to 49 per cent of those in his private practice.

TABLE 20 —INCIDENCE OF DIABETES IN THE FAMILIES OF DIABETICS PERCENTAGE OF CASES REPORTING HEREDITARY AND/OR FAMILIAL TYPES OF FAMILY HISTORY. RECENT CLINICAL EXPERIENCES

	No of Cases	*Per Cent with Family History of Diabetes*
Joslin, total children, 1957	4054	41 6
Joslin, 1957 Children of 20 or more years' duration	1072	57 0
Joslin, 1941 Hospital cases	1619	41 0

At medical meetings during the last twenty years we often distributed ballots and asked for reports of heredity among the audiences composed largely of doctors and medical students with a lesser number of nurses and dietitians. The average incidence for all groups was 22 3 per cent In a recent questionnaire of 68 nurses in training, 35 per cent reported that they knew of diabetes among their relatives

A EVIDENCE IN FAVOR OF THE THEORY THAT DIABETES IS INHERITED

PRISCILLA WHITE, M D

The evidence in favor of the theory that the potentiality for developing diabetes is inherited rests primarily upon five facts· (1) The concordant occurrence of diabetes in similar twin mates, (2) the statistically greater

trait

[5] Blotner and Hyde New England Jour Med , *229*, 885, 1943
[6] Blotner Jour Am Med Assn , *131*, 1109, 1946
[7] Rathery Loc cit , p 47

Diabetes in Twins.—The occurrence of diabetes in twins has been mentioned many times in the literature.[8] This has suggested inheritance, because 80 per cent of twin cases reported were similar in type. Much can be learned also from a comparative analysis of the incidence of diabetes in similar and dissimilar twins, for, if diabetes is inherited, the incidence of the disease in both members of pairs of similar twins should far exceed the incidence in dissimilar twins. The expected incidence of diabetes among pairs of similar twins would eventually be 100 per cent. The expected incidence of diabetes in both members of pairs of dissimilar twins, all other things being equal, would be not more than that of ordinary brothers and sisters of diabetics. In the authors' series of patients, 96 pairs of twins suitable for analysis were found. Of these twins, 33 were similar in type, 63 dissimilar. Many other pairs of twins were found in the total group of diabetics, but were excluded because of death of one of the pair in infancy or very early childhood.

Among at least 16 of the 33 sets of similar twins, both were diabetic (48.5 per cent) whereas in only 2 (3.2 per cent) of the 63 pairs of dissimilar [illegible]

twin group being perhaps slightly greater, because 10 per cent of their parents were diabetic, compared with 5 per cent in the similar twin group, 9 per cent in the diabetic population and 2 per cent in the control population [illegible]

[illegible] was performed on the twin mate who had no positive clinical evidence of diabetes. Among similar twins Berg found 17 pairs absolutely concordant, 13 others concordant according to tolerance test and 16 were probably discordant, or in a total of 65 per cent both twin mates had contracted diabetes. Of the dissimilar twins 9 pairs were concordant with clinical manifestations of the disease, 9 twin mates had lowered glucose tolerance and 62 pairs were probably discordant, or in 22 per cent both dissimilar twin mates had contracted diabetes. After the age of forty-three all similar twins studied by Berg were concordant. This was not true of our patients [illegible]

[illegible]diabetes is likewise hereditary, because its character in the twins was iden-

[8] Curtis: Jour. Am. Med. Assn., 92, 952, 1929. White: Diabetes in Child[illegible] Umber: Jour. Am. Med. [illegible] 359, 1933. Watson: Canad. [illegible] Human Heredity, New York, [illegible]

[9] Berg: Jour. Am. Med. Assn., *112*, 1091, 1939.
[10] Umber: Klin. Wchnschr., *19*, 45, 1940.

of all those influences

od Relatives of Our Patients.—The incidence of diabetes in the parents and siblings of diabetics was found to differ significantly from the incidence of diabetes in the parents and siblings of non-diabetics. This statement is based upon the analysis of a total of 4434 parents and siblings of diabetics and 1290 parents and siblings of non-diabetics. The total incidence of diabetics in the diabetic population was 300, or 6.7 per cent, compared with 16, or 1.23 per cent, in the control non-diabetic population. This difference between the incidence *of diabetes in blood relatives of diabetics and of the control population is* statistically significant.

Among 1,741 relatives of diabetics Ford and Glenn[11] found 73 undiagnosed diabetics, an incidence of 4 per cent, which was 5 times greater than the incidence found in their control population. A further statistically significant deviation from random occurrence was found when the incidence of diabetes in parents and siblings was compared decade by decade with controls. Twenty-three per cent of diabetic families reported diabetic relatives other than parents or siblings, compared with 11 per cent of non-diabetic families who reported such diabetic relatives. Umber[12] found heredity in 26 per cent of 3500 of his cases, in contrast to 2.8 per cent in a control population numbering 1000. Cammidge[13] found 3.4 per cent of 500 non-diabetics with a family history of diabetes, and Kern[14] found 6.2 per cent in 500 non-diabetics.

Actual and Expected Incidence in Direct Ancestry of Diabetic Children.—The actual and expected incidence of diabetes in the parents and grandparents has been studied for child diabetics by Joslin, Dublin and Marks.[15] They computed the expected number of diabetics among the

between 1920 and 1934 and whose heredity record includes diabetic relatives reported up to May, 1935, 152 had diabetic parents or grandparents

4.3 per cent.

In comparison with the 175 cases actually recorded, only 99 were expected to be diabetic on the basis of the 1930 mortality statistics and 72

[11] Ford and Glenn. South. Med. Jour., *44*, 239, 1951.
[12] Umber. Med. Welt, *9*, 889, 1935.
[13] Cammidge. Lancet, *1*, 393, 1934.
[14] Kern. Trans. Assn. Am. Phys., *49*, 23, 1934.
[15] Joslin, Dublin and Marks. Am. Jour. Med. Sci., *193*, 8, 1937.

where the basis for grandparents was the 1910 mortality statistics. These figures indicate an incidence of diabetes among parents and grandparents at least twice that expected in a random sample.

Demonstration of Mendelian Ratios of the Recessive Type.—Non- [illegible]

[illegible] incidence of diabetes among the parents of their patients. The genealogies in the literature reported by Bauer, Fischer and Lenz,[16] as well as our own, support the notion that diabetes often skips a generation. If diabetes were transmitted as a dominant trait, eventually one parent in each family of our patients would be diabetic. According to the age behavior of diabetes (see page 52), about 50 per cent of the parents at the median age of the [illegible]

[illegible] explains pseudo-dominance as follows: "Because the penetrance of diabetes is 20 per cent, 10 out of [illegible]"

[illegible] Non-diabetics were designated as Mm or MM. Three types of mating can produce mm offspring:

1. Mm × Mm = 1 MM : 2 Mm : 1 mm
2. Mm × mm = 1 Mm : 1 mm
3. mm × mm = 1 mm

The expected ratios may be altered by many factors, including the family size, the age at onset of diabetes, the chances of dying before the age at [illegible]

[illegible] The expected number of diabetics among siblings in our diabetic cross (mm × mm) remained 100 per cent, in the diabetic-carrier cross (Mm × mm) became 40 per cent, and in the carrier-carrier (Mm × Mm) cross, 16 per cent.

b. Effect of Age Behavior.—Unlike many traits subject to genetic analysis diabetes is not manifest at birth but appears at all ages from infancy to more than ninety years. The identification of all diabetics cannot be completed until age ninety has been achieved by all members of the family. Not one of the authors' families satisfied this condition. On

[16] Bauer, Fischer and Lenz: Human Heredity, New York, The Macmillan Co., 1931.

[17] Hanhart: Investigations carried out under the auspices of Nordisk Insulin Fond, Zurich, Switzerland. (Paper unpublished.)

the basis of age at onset of diabetes the expected ratios could be only partially fulfilled. Four per cent diabetics were found where 16 per cent were expected, 10 per cent where 40 per cent were expected and 24 per cent where 100 per cent were expected. Ninety-eight diabetics appeared in 2300 siblings of the carrier × carrier cross, 48 in the 175 siblings of the diabetic × carrier cross, and 8 in the 33 children of the diabetic × diabetic cross. One quarter of the expectation was fulfilled in each instance. The ratios were almost identical: 1:2 5:6.1 expected and 1:2 4:5.7 observed. Furthermore, the median age of these groups lies in the fifth decade, at which time 25 per cent of all potential diabetics should be identified.

c EFFECT OF CHANCES OF DEATH BEFORE ONSET OF DIABETES —The third variable concerns the evaluation of the chances of death before the onset of diabetes. Here one assumption was made, namely, that the predestined diabetic, before the development of the disease, lives and dies at the same rate as those persons not predestined to diabetes. No evidence has appeared that prediabetics or their relatives resist any disease process. From ordinary life tables, and tables giving diabetes age incidence for each decade we have, therefore, calculated the proportion of potential to identifiable diabetics Glover's life tables for 1910 for the population of the United States and diabetic incidence data from these sources were used, as follows: *the first 6000 diabetic cases of the Joslin series, data of Adams from the* Mayo Clinic, and the actual incidence among the patients of this study. It was demonstrated[18] that from these three sets of onset data essentially similar life tables for potential diabetics are derived The expected number of *mm* individuals actually identifiable as diabetics was calculated by multiplying the Mendelian expectation by the expectation of identification. When this is done, the expectation in a group of 523 cases so analyzed is closely fulfilled

Thus in the group where neither parent had diabetes, 64 of 1495 siblings of the patients were diabetic, as compared with 64 68 identifiable on the data of Joslin, 68 35 on the data of Adams, and 64 68 on the population studied Among the siblings of patients with one parent diabetic, 32

analysis an objection may be raised, because, while it is true that once

[18] Pincus and White Am Jour Med Sci, *186*, 1, 1933

[19] Joslin Treatment of Diabetes Mellitus, 6th ed, Philadelphia, Lea & Febiger, 1937. See also Am. Jour Med Sci, *188*, 159, 1934

contains 100 too few diabetics. The diagnosis of diabetes had been omitted accidentally in 24 per cent of the cases. Other diseases had precedence in 13.5 per cent. Estimates of incidence of diabetes accounting for sex frequency and using the two sets of data on incidence showed that only 12 unidentified diabetics among the parents are derived from Joslin's incidence data, whereas 175 are derived from the Massachusetts Life Table,[20] it was found that the expected and observed number of diabetic siblings agreed fairly well even when we used two definitely different estimates of diabetes onset incidences (Table 21).

TABLE 21.—EXPECTED NUMBER OF DIABETIC SIBLINGS WHEN 175 UNIDENTIFIED GENETICALLY DIABETIC PARENTS ARE REDISTRIBUTED IN THE CALCULATIONS INVOLVING THE MASSACHUSETTS INCIDENCE DATA

Type of Cross	*Expected Diabetic Siblings Based upon Joslin's Incidence*	*Expected Diabetic Siblings Based upon Massachusetts Incidence*	*Diabetic Siblings Observed*
Mm × Mm	121	90	98
Mm × mm	63	39	48
mm × mm	13	8	8

c. DEGREE OF ACCURACY OF DIAGNOSIS AND CONSIDERATION OF POTENTIAL DIABETICS.—Still another theoretical source of error exists and another

curves do not preclude the future development of diabetes

One hundred and sixty-nine close relatives of diabetics and 125 control individuals were studied by random blood sugars or tolerance tests. In many instances the tests confirmed case histories, but relative hyperglycemia was characteristic of the families of diabetic individuals no matter whether the examination was by random or by tolerance test. Among the blood relatives of diabetics, 14 per cent by random, 25 per cent by tolerance test had above normal values, compared with 2 per cent in the control population. These somewhat elevated values may not be clinically abnormal but are statistically above normal[21] in this series

Demonstration of Mendelian Recessive Ratios in Presumably Latent Diabetics.—The proportion of hyperglycemic individuals in the three types of mating was found to approximate closely simple Mendelian recessive probabilities, 1 : 2 : 4. The percentages were 7, 18 and 25 in the carrier × carrier, diabetic × carrier, and diabetic × diabetic cross, respectively, and these percentages are in the ratio, 1 : 2.6 : 3.7. The ratios of presumed diabetics on the basis of Joslin's onset data are 1 : 2.2 : 3.9, and on the basis of Massachusetts tables, 1 : 2.1 : 4.7.

[20] Pincus and White. Am. Jour. Med. Sci., 188, 159, 1934.
[21] Pincus and White. Ibid., 188, 782, 1934.

If we assume that these hyperglycemic individuals do represent future diabetics, the actual and estimated number of cases added to clinical diabetics give us the number of diabetics identifiable at approximately fifty years of age, whereas the median age of this group is thirty-five years. Will our blood-sugar examinations enable us to foretell by many years the future diabetics? See page 53.

The blood sugar of siblings of young diabetics was studied by Mackler and Fischer and gave negative evidence.[22] Since these examinations were made in a pediatric service, the youth of the individuals tested must be taken into consideration. Tyner[23] found that prediabetics were more frequent among those with a family history of parental diabetes. Sherrill[24] reported 21 abnormal curves in 40 supposedly normal relatives of diabetics. Pannhorst[25] studied 26 descendants of diabetics and found 11 showed anomalies of carbohydrate metabolism. Steiner,[26] Pannhorst,[25] Rudy and Keeler[27] have reported the incidence of diabetes in the offspring of certain crosses. Lemser[28] has investigated relatives of diabetics with carbohydrate tests, noted abnormal but not distinctively diabetic curves and regretfully points out the inadequancy of present methods, but emphasizes the necessity of following up such individuals. We cannot, however, compare their reports with our own since no corrections could be made for manner of selection, number of children, age behavior or chances of identity by survival.

Incidence of Diabetes in Genealogies of Diabetics Behaves Like a Mendelian Recessive Trait.—Three-hundred-four genealogies of diabetic patients of the Joslin Clinic and 110 genealogies of normal individuals were compared by Professor Ernst Hanhart.[29] Among 18,493 members of diabetic families, 975 diabetics were reported, an incidence of 5.3 per cent. Among 6,042 members of the normal families the number of diabetics was 74, or 1.2 per cent.

That the heredity of the diabetic trait is predominantly a simple recessive is statistically substantiated in this group by the finding (1) that the incidence of diabetics in the siblings of the diabetic population was 27.3 per cent and (2) that in the offspring of the diabetic population it was 22.0 per cent. (Both of these figures were obtained by correcting statistically the actual incidence for the age behavior of diabetes.) Among the children of 35 instances of conjugal diabetes studied by Hanhart 114 were over forty years of age. Of these 39 were diabetic, 94 per cent of the number expected for their age.

Colwell,[30] Woodyatt,[31] Penrose and Watson,[32] approaching the problem differently, present data favoring the theory that the tendency to develop

[22] Mackler and Fischer. Jour. Am. Med. Assn., *103*, 240, 1934.
[23] Tyner. Amer. Jour. Med. Sci., *185*, 704, 1933.
[24] Sherrill. Jour. Am. Med. Assn., *77*, 1779, 1921.
[25] Pannhorst. Verhandl. d. deutsch. Gesellsch. f. inn. Med. XLVIII Kongress Wiesbaden, p. 411, 1936.
[26] Steiner. Deutsch. Arch. f. klin. Med., *182*, 231, 1938.
[27] Rudy and Keeler. New England Jour. Med., *221*, 239, 1939.
[28] Lemser. Munch. med. Wchnschr., *85*, 1657, 1938.
[29] Hanhart. Loc. cit., p. 51.
[30] Colwell. Arch. Int. Med., *70*, 523, 1942.
[31] Woodyatt and Spetz. Jour. Am. Med. Assn., *120*, 602, 1942.
[32] Penrose and Watson. Proc. Amer. Diabetes Assn., *5*, 163, 1945.

diabetes is inherited. Thus, Colwell states that if one employs the amount of insulin required daily for uniform control as a gauge of the severity of

[illegible]

reemphasize, as did Bence-Jones in 1865,[33] Naunyn [34] and von Noorden and Isaac[35] later, the anticipation of diabetes When diabetes occurs in three generations of a single family it may appear earlier in the second than in the first and earlier in the third than in the second, the same trend continuing through three generations, also it can be exhibited to some extent between older and younger members of a single generation. When an in-

[illegible]

error in determining actual ages of onset in 79, positive but less certain in 85, and suggestive in 90 or 100 families in which the disease occurred in two or more generations

However, at the Mayo Clinic, Steinberg and Wilder[36] reanalyzed the significance of anticipation among 200 diabetic families and concluded that the

[illegible]

dence of diabetes in like sex siblings

LINKAGE OF GENES —No positive evidence of sex linkage has been demonstrated That one or more factor pairs may be involved in diabetic heredity is suggested by the high incidence of obesity, of congenital defects especially of mesenchymatous tissue (first reported by Priesel and Wagner), possibly [illegible]
betic pat
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f [illegible] per cent for all males, whereas among females the incidence in Jewish cases was 29 1 per cent, compared to 26 5 per cent for all females The higher incidence of family histories of diabetes among Jewish patients has been consistent throughout the experience The incidence of hereditary type histories at younger ages is definitely

[33] Bence-Jones Medical Times and Gazette, 1, 58, 1865
[34] Naunyn Der Diabetes Mellitus, Wien, Alfred Holder, p 37, 1906
[35] von Noorden and Isaac Die Zuckerkrankheit, 8th ed, Berlin, Julius Springer, 1927
[36] Steinberg and Wilder Proc Staff Meet Mayo Clin, 25, 625, 1950, Ann. Int Med 36, 1285, 1952, Am Jour Human Genetics, 4, 113, 1952
[a] Dublin and Marks Am Jour Med Sci, 193, 8, 1937

higher among Jewish than non-Jewish patients, whereas at older ages the reverse is true.

Among Jewish children the percentage of positive family histories is higher than among adults. Of 80 Jewish children, 34 (42.5 per cent) reported cases of diabetes in their families Hereditary type histories predominated, being reported by 35 per cent

Muller,[38] Finke,[39] and Priesel and Wagner[40] report 33 per cent, 25.4 per cent, and 48 per cent respectively of Jewish diabetic patients as having diabetic relatives. Rudy and Keeler[41] report that 6 3 per cent of 1000 non-diabetic Jewish patients had diabetic heredity in contrast to 1.23 per cent in our unselected control group. However, 29.1 per cent of 1037 Jewish diabetic patients had one or more relatives with the disease as compared with 6.7 per cent in our unselected series A study of blood groups (O, A, B and AB) and blood types (M, N and MN) was made The distribution showed no significant difference from the distribution in non-diabetic Jews. In general the distribution of blood groups in all Jews in Boston most closely corresponds to that reported for groups of Jews in Russia

Zeytinoglu[42] studied 10 families for blood groups No one group predominated, but diabetic parent and child and siblings showed the same group in 81.5 per cent.

The behavior of diabetes continues to challenge geneticists Among disabling and crippling disorders, elimination is the rule This characteristic has not been true of diabetes in spite of the tendency toward elimination through the high fetal wastage of diabetic females and the frequent occurrence of impotency in the young diabetic male

The high frequency of the recessive gene or genes producing diabetes ... in view of the strong ... ears The *frequency* ... bout 05" and pene- ... "about 1 per cent" in the United States today) is far higher than can be explained by any *known mutation rate*

...

precocious growth and sexual maturity can be demonstrated in children of the homozygous "diabetic genotype" several years before they develop diabetes, so that the precocity can be attributed to pleiotropy and dis-

[38] Müller Med Klin, *31*, 277, 1935
[39] Finke Ztschr f klin Med, *114*, 713, 1930
[40] Priesel and Wagner Die Zuckerkrank u ihre Behand im Kindersalt, Leipzig, George Thieme, P 121, 1932
... d, *221*, 239, 1939

... ence, Philadelphia, Lea and Febiger, 1932
[45] White Diabetes, *5*, 445, 1956
[46] Wagner, White and Bogan Am Jour Dis Child, 63, 667, 1942
[47] Ditzel, White and Duckers Diabetes, *3*, 99, 1954

sociated from the abnormal or pathological effects of disease, it would

those having serious illness other than diabetes prior to age 20 Birth dates ranged from 1915 to 1938

comparable group known abroad is that of 2,590 English students reported by Ellis[50]

TABLE 22 —MENARCHIAL AGE IN FOUR GROUPS

	No	*Mean Age*	*S E*	*Sigma*
Diabetes Onset at 18 or Over	201	12 84	± 098	0 39
Diabetes Onset before 11	222	14 14	± 126	1 89
Cincinnati, born in 1919	216	13 09	± 049	0 77*
Southern England	2,590	13 49	± 01	1 19

*By computation, taking "sigma" as the product of "standard error" times the square root of the number of cases

Mills[51] has published average menarchial age for large groups of students of separate years of birth, ranging from 1911 through 1922, from four universities The lowest means of annual groups from the other three are as follows

	No.	*Mean Age*	*S E*	*Sigma*
North Carolina, born in 1918	669	13 31	± 030	0 776*
Kansas, born in 1919	295	13 15	± 049	0 842*
Wisconsin, born in 1921	775	13 22	± 030	0 835*

(*By computation, taking sigma as the product of standard error times the square root of the number of cases)

Satisfactory demonstration that persons with the homozygous "diabetes-producing genotype" reach sexual maturity at significantly earlier ages than others would suggest a higher "adaptive value" (in the Darwinistic sense) of this genotype, particularly in primitive economies, and would therefore

[48] Post and White Diabetes, 7, 27, 1958.
[49] Mills Human Biology, 13, 363, 1941
[50] Ellis Brit Med Jour, 1, 86, 1950
[51] Mills Loc cit p 57

who developed diabetes at 18 or over (Table 23)

TABLE 23.—AGE OF INCEPTION OF THE MENARCHE IN TWO GROUPS OF DIABETICS BY YEAR OF BIRTH

Birth Year	*Diabetes Onset 18 or Over* *No*	*Mean Age*	*S E*	*Diabetes Onset Before 11* *No*	*Mean Age*	*S E*
1915	6	12 722	25			
1916	8	12 833	15			
1917	9	12 296	.14			
1918	14	12 870	.13			
1919	9	13 167	.12			
1920	20	13 054	11	9	15 324	.17
1921	17	12 809	10	7	13 655	35
1922	9	13 065	06	12	15 625	.15
1923	18	13 074	07	13	14 996	12
1924	14	13 619	.18	11	14 295	12
1925	14	12 452	08	10	14 9	13
1926	11	13 144	10	11	13 5151	16
1927	14	12 798	08	9	14 852	28
1928	5	12 717	07	8	14 292	25
1929	13	12 955	09	6	13 958	.25
1930	7	12 369	18	11	13 947	.17
1931	7	12 190	.16	12	13 472	09
1932	8	12 812	16	6	13 236	.18
1933	2	13 417	12	14	13 054	.11
1934	3	11 194	43	12	13 208	.11
1935	3	12 5	60	12	12 902	09
1936	1	13 583		21	14 014	08
1937	1	13 25		14	13 619	15
1938	2	13 420		18	13.315	15
1939–1941	1	12 667		8	12 786	.19
	216			224		

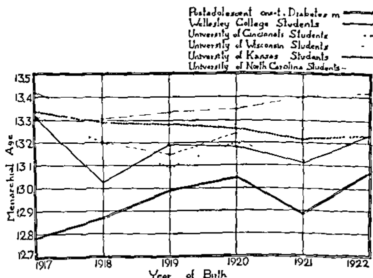


FIG. 4.—Menarchial Ages of Girls Diabetic at 18 or over, compared with five Student Groups, subdivided by Year of Birth [46]

Eugenics.—Steinberg[52] has made predictions for the chances of developing diabetes. When both parents have diabetes, the chances of developing it are 100 per cent; when one parent has diabetes and on the other side a

parent has diabetes or grandparents who are spouses are diabetic, the chances are 22 per cent, a grandparent alone, 14, and when a first cousin is diabetic, the chances are 9 per cent

Prevention of Diabetes —The protein chemists may eventually alter the chemistry of the gene, but at the moment our theories concern the prevention of diabetes by prevention of the precipitating factors. The following have appeared to be important obesity, the most common factor in the adult population, rapid linear growth in the juvenile just prior to onset, certain endocrine changes associated with puberty, pregnancy, the menopause and infections Lessening the effect of these stresses by some form of treatment is now advocated

The concept of protecting the individual who is susceptible to diabetes during such episodes as have been described has been advanced most aggressively by Hoet[53] He has an ingenious program. Of the conditions

glucose tolerance tests at that time of pregnancy when the production of the placental diabetogenic hormones (growth hormone, ACTH and corti-

of pregnancies but also for the production of congenital anomalies For this reason he recommends a provocative glucose tolerance test at about the fourteenth week of pregnacy, at which time the placental production of the

but it is most certainly not borne out in its entirety in our experience We investigated a group of children of diabetic mothers and 23 per cent had clinical diabetes requiring insulin, or had positive glucose tolerance tests, exactly the same type of children, offspring of young diabetic fathers, were found to have clinical or chemical diabetes in 21 per cent The offspring *of two diabetic parents had clinical or chemical diabetes* in 62 per cent of the cases Again the Mendelian recessive hypothesis is fulfilled Our incidence of 21 and 23 per cent diabetes when one parent is diabetic closely approximates Steinberg's prediction of 22 per cent However, Hoet's

[52] Steinberg Loc cit p 56
[53] Hoet Diabetes, 3, 1, 1954

scheme of protecting the prediabetic woman during pregnancy is certainly challenging and a program which should be adopted at least in part by all and translated to the other possible situations where latent diabetes may be revealed, such as infections, etc. Programs may include any of the following alone or in combination—regulated diet, insulin or insulin substitutes.

Geneticists have proposed another concept which requires re-evaluation of our thoughts in relation to inherited diseases, namely, that the carrier of the disease will show the disturbed chemistry in part. This has been demon- [illegible] the parent of an [illegible] which is similar [illegible] When we translate this experience to diabetes and either do a simple provocative or a cortisone glucose tolerance test, the number of positive reactors among the children or parents of diabetics is high and at the moment we are unable to say whether a positive glucose tolerance test represents prediabetes or merely reveals the carrier tendency. One difference may be the degree of the abnormality. [illegible] tests rise to such [illegible] those whose gluc[illegible] normal may represent the carriers. At the moment only time will reveal the true state

Attempts to Cure Diabetes.—Curable forms of diabetes exist. This is particularly true of Cushing's disease, pheochromocytoma, possible acromeg- [illegible] cal evidence of [illegible] have the pos- [illegible] as these cases are, however, they represent a very small number of total diabetics.

Pseudo-cures sometimes confuse us During the course of diabetes, almost exclusively in female patients, rarely in males, spontaneous hypoglycemia is reported These patients state that during the course of time, often rather quickly, their insulin requirement drops from the typical level to but a few units and, finally, that it has been necessary to omit insulin Subsequently they experience all the symptoms of hypoglycemia Upon [illegible] es, while on a [illegible] cemia When [illegible] nce they have [illegible] teen years of [illegible] She entered *the hospital for investigation.* Daily the 24-hour specimen was *found* sugar free It happened that at the time one of us was carrying on metabolic studies and this interesting case was included When her 24-hour specimen showed no glucose, but also no nitrogen and no creatinine, malingering was suspected She was never parted from her pocketbook, which was finally suspected as the source of her hypoglycemia The separation was achieved. In her bag was found not only her insulin kit, but [illegible]

altering the endocrine balance. This has been achieved through medical or surgical hypophysectomy. However, replacement therapy necessarily makes the disease reappear in part. For medical or surgical adrenalectomy the same statement holds true Thyroidectomy, medical and surgical, by lowering the metabolism alters the disease in part, but since myxedema is also associated with atherosclerosis, this may lead to situations which are fully as malignant as diabetes itself.

Attempts to protect islet tissue have been made Simultaneously in this country Brush[54] working with juveniles and Umber in Germany with adults recommended overinsulinization of the patient at the start of treatment It is an interesting concept Its scientific support appeared after these workers suggested this mode of treatment, for in Best's laboratory in Toronto and in Lukens' in Philadelphia, it was found that rest of the pancreas in experimentally produced diabetes brought about disappearance of clinical signs of the diabetes and return to histologically normal islet tissue However, enough time has elapsed to note that this interesting concept has not been fruitful as far as reversing or altering the course of diabetes

Stimulation o[illegible]
or extirpation [illegible]
deTakets[55] man[illegible]
altered

USE OF FEMALE SEX HORMONES —Houssay's experiments have been most suggestive [illegible]

[illegible] rats[56] This behavior suggested that the female sex hormone might be an islet protective substance The hypothesis was studied further by the injection of both male sex hormone and female sex hormone. The administration of male sex hormone accelerated the process, but when a female sex hormone, estradiol, stilboestrol, etc was used along with insulin, diabetes was postponed or, if present, was reversed Examination of islet tissue showed islet hypertrophy and islet hyperplasia When pellets of estradiol were implanted into the pancreas, the islets in relation to these substances were fou[illegible]
most hyperplastic [illegible]
insulin content of th[illegible]
same fashion Compound F, cortisone in very small doses, thyroxin and estrogen were tested and were found to be antidiabetic substances A group of our patients were accidentally subjected to the same experiemnt The management of the diabetic pregnant woman in our clinic has included large doses of female sex hormones, both estrogen and progesterone A group of former juvenile patients, who during pregnancy were treated in this fashion, showed something which had not been noted before Fifty per cent showed a 50 per cent drop in insulin requirement, which has held for some ten years, and 20 per cent showed a 75 per cent drop One such

[54] Brush Am Jour Dis Child, *67*, 429, 1944
[55] Wilder and de Takats Jour Am Med Assn, *93*, 606, 1929
[56] Houssay Brit Med Jour, *2*, 505, 1951

patient showed islet hypertrophy and hyperplasia eight days after delivery. In a recent study of the 1072 juvenile patients who have survived twenty years or more of their disease, only 5 per cent of the males showed this 50 per cent drop

Subsequently these patients have been studied for response to the sulfo-

pregnancy may be due to inhibition of the antagonists or greater utilization of either glucose or insulin.

A further attempt to duplicate the Houssay[47] experiment was made in some sixty juvenile patients, for the most part those who had reached the favorable remission phase They were treated with either small doses of thyroid, 0 1 mg thyroxin, or doses of cortisone which compared with those used by Houssay and his co-workers in animal experiments, from 2 5 to 15 mg. daily. The natural course of diabetes continued in the younger group b

best ca

taking

years the remission phase would normally have disappeared and intensifica-

reporting every one to three weeks and has actually been followed better

Pancreatic Grafts —The final attempt to change the course of diabetes has been through the use of pancreatic grafts It is well known that the most favorable subjects for grafting experiments are (1) patients who are identical twins and (2) patients with agammaglobulinemia An identical twin would be of no value in diabetes, because the second twin, if not a revealed diabetic, is at least a potential diabetic There are ways for producing agammaglobulinemia, but this is not desirable in diabetes where one of the greatest problems is poor resistance to infection From the point of view of grafting, the pancreas of a newborn non-surviving infant of a diabetic mother is potentially desirable Fetal pancreas is ideal for it consists merely of endocrine and no exocrine function, there is no digestive

[47] Houssay Loc cit p 61

that gamma globulin and similar substances could not penetrate and destroy the islet cells and yet the insulin would penetrate Technically there was no foreign body reaction and we assume that the grafts have merely atrophied and probably have been absorbed The first patient, where the entire pancreas was transplanted, was done in 1955 and we have subsequently delivered her of a surviving infant. Tested with sulfonylurea she showed no response to the test dose used

This group is tested at three-month intervals and at the moment results are equivocal. It takes six months for the pancreas to grow We do not expect success in the five done to date Blood groups are not always com-

tinue to stimulate these efforts to alter the course and outcome, especially in the young patients The remission phase appears to be the ideal period for these continued efforts

B OBESITY AND DIABETES[33]

ELLIOTT P JOSLIN, M.D

An Intimate Illustration of the Relation of Obesity and Diabetes.—Heredity determines the susceptible individuals, but since the disease is rarely present at birth, search must be made for precipitating factors which will help to bring out the inherited disposition Of all these factors obesity is by far the most important For this we should be grateful, because obesity is preventable

Our attention was definitely focussed upon the etiological importance of obesity in diabetes by two sources of evidence The senior author was brought up in a country town in New England, and in it he found the first

lies—and of this number all but 1 subsequently succumbed to diabetes.

local and state boards of health if these deaths had occurred from scarlet

noticed Even the insurance companies failed to grasp their *significance*, and yet probably no group of individuals in the community carried *per capita* a higher amount of insurance than did these 6 diabetics At the time these individuals lived, ideas of exercise for pleasure and the benefit

[33] The heights of adult diabetics are normal For data about children see page 714

of the body had not penetrated this rural region. Consequently, in this, as in many other New England villages, fortunately to a less extent now, the well-to-do were unusually fat.

Statistical Relations Between Obesity and Diabetes, an Analysis of 1000 Diabetics.—While compiling the data for age, height and weight of a series of 118 diabetics whose respiratory metabolism had been studied at the Nutrition Laboratory of the Carnegie Institution, it was found that [illegible] weight [illegible] were [illegible] ses of diabetes for whom the age, date of onset of the disease, weight and height were known, were compiled and such are recorded in Table 24

From this table the statement is justified that among 1000 successive diabetics the maximum weights of only 8 per cent were below the standard weight zone, whereas 15 per cent were in that zone, and 77 per cent were above it Between the years fifty-one and sixty there were but 2 diabetics in 252 whose maximum weights were below the normal zone prior to the onset of the disease. Among 2000 of our own cases of diabetes not one occurred who was more than 30 per cent under weight, and in Adams' series of 1000 cases at the Mayo Clinic no patient developed the disease who was more than 20 per cent underweight. From 31 years onwards 79 to 89 per cent of our cases were overweight.

TABLE 24 —VARIATION FROM NORMAL OF MAXIMUM WEIGHTS AT OR PRIOR TO ONSET OF 1,000 CASES OF TRUE DIABETES, CALCULATED FOR HEIGHT, AGE AND SEX

Age, Years	*Number of Cases*	*Percentage in Normal Average Zone (+5 to −5 Per Cent)*	*Percentage of Each Decade*	
			Below Standard Weight	*Above Standard Weight*
0 to 10	43	37	44	19
11 to 20	84	39	29	32
21 to 30	112	19	10	71
31 to 40	172	6	5	89
41 to 50	244	12	3	85
51 to 60	252	12	1	87
61 to 70	79	10	6	84
71 to 80	14	14	7	79

Analysis by the Statistical Bureau of the Metropolitan Life Insurance Company of 4596 of the Authors' Diabetics —For a period of thirty years, 1898–1928, our clinical records were analyzed with the help of Dr Dublin and Mr Marks, of the Metropolitan Life Insurance Company,[49] from two points of view (1) The maximum weight prior to onset of the disease, and [illegible]

close to 60 per cent of the women were at least 20 per cent overweight at

[49] See reference 1, p 47

their maximum weight Large numbers were extremely fat. No less than 16 5 per cent of the men and 25 8 per cent of the women were 40 per cent or more overweight at their maximum In all groups there is a greater frequency of overweight among diabetic women than among men In contrast to these high figures, only 7 9 per cent of the diabetic men and 6 3 per cent of the diabetic women had always been underweight (5 per cent or more less than average for age) and less than 1 per cent of the whole group had always been 20 per cent or more underweight.

In Jewish adult patients, the tendency to obesity is even more marked than among other patients The proportion of diabetic Jewish men who were overweight at their maximum prior to diagnosis was 86.8 per cent, compared with 78 5 per cent for all adult males in this experience Among Jewish women, no less than 94 3 per cent were overweight at their maximum compared with 83 3 per cent for all female diabetics. More of the Jewish patients were very stout, particularly the women Of the diabetic Jewish men, 58 4 per cent were at least 20 per cent overweight as against 51 per cent for total males, and of the Jewish women, 77 per cent, compared with 59 3 per cent for total females The proportion of the actually obese (40

cent for all of the diabetic women Only 2 of the Jewish adult patients had always been thin, 1 male and 1 female, both of whom were under age thirty-five years at onset It is my impression that Jewish patients are today far less apt to be fat than a generation ago Data from Israel should help to answer this question

Diabetic children, in contrast to adults, are usually not overweight This was noted by Root, White and Joslin in 1925 and has been repeatedly confirmed by others In the child overgrowth is vertical, in the adult it is lateral Is not each type of endocrinal origin?

Travie[136] found that obesity preceded diabetes in 83 per cent of 1500

patients The cholesterol and uricemia tended to increase long before hyperglycemia appeared

Development of Diabetes Among Persons Accepted for Insurance.— The importance of obesity in diabetes is also confirmed by insurance records, which show that its subsequent development among persons accepted for insurance after medical examination and known not to be diabetic is far more frequent among overweights than among persons of average weight or less Thus, in the Medico-Actuarial Investigation, covering the combined mortality experience of 43 insurance companies, between 1885 and 1900

broad

weight

betwe ... among those insured at ages under thirty

[136] Travie Diabète, 4, 249, 1956

years, the subsequent diabetes death-rate of overweights was 15 per 100,000 compared to 6 among "standard" weights and 2 among underweights. Among those between thirty and forty-five years when insured, the diabetes mortality was 59 per 100,000 for the overweights, 12 for "standard" weights and 5 for underweights For those forty-five years or over when insured, the diabetes death-rate among overweights was 136, compared with 28 for the "standard" group and 6 for the underweights. In this study, therefore, a large disparity existed between the diabetes death-rates of overweights and persons of average weight or less, and this disparity increased with advancing age. In another Medical Impairment Study, an investigation of the same type as the earlier one, but covering the experience of 39 companies, between 1909 and 1927, similar results were obtained.

Liability to Diabetes Increases With Degree of Overweight—Furthermore, the toll of diabetes increases with the degree of overweight. A study of the experience of the Union Central Life Insurance Company[60] showed that men who were 5 to 14 per cent above average weight had a diabetes mortality only one and a half times that of normal weights, compared with three and a fifth times for those 15 to 24 per cent overweight, and eight and a third times for those 25 per cent or more overweight. These differences were even larger at the ages of forty-five years and over; those 5 to 14 per cent overweight suffered a mortality nearly twice that of normal weights, and those 15 to 24 per cent overweight, nearly four times, while those 26 per cent or more overweight had a mortality over ten times that of average men

Similar studies on women show the same characteristics.[61]

Obesity and Heredity Closely Linked.—All fat people do not, of course, get diabetes For example, in the Medico-Actuarial Investigation, only 5 per cent, 1 in 20, of the deaths of men 50 pounds or more overweight when insured were recorded as due to diabetes We do not accept this figure as portraying the whole truth It may be explained by the fact that the diabetes of the obese is apt to be mild and that the Lombard and Joslin correction would prevail here even more than among all diabetics. A detailed study of 1000 such cases would be a field for investigation Other factors must be involved in the causation of the disease. Indeed, the factors of obesity and heredity are probably closely linked Obese persons who become diabetic appear to be those with an inherited susceptibility to the [illegible] he disease [illegible] many careful [illegible] in the earlier part of this chapter It is also indicated by Tyner's study[62] of the weights of 500 patients with normal carbohydrate tolerance and 500 with impaired tolerance, but not frankly diabetic Tyner found that "prediabetes" was more common in obese persons than in those of normal weight only where there was a family history of diabetes The studies of Conn and Fajans[63] support this idea (See page 54) Thompson[64] has

[60] Dublin and Marks Human Biology, *2*, 159, 1930
[61] Dublin and Marks Proc Assn Life Ins Med Directors of Am *24*, 47, 1937 *25*, 203, 1938
[62] Tyner Am Jour Med Sci, *185*, 704, 1933
[63] Conn and Fajans Ann Rev Physiol, *14*, 465, 1953
[64] Thompson *et al* Canad Med Assn Jour, *63*, 556, 1950

the need for meticulous study of the heredity and non-heredity, borderline cases of diabetes. Possibly, in Sweden where each individual has an identification number with date of birth, and in some sections where diabetics report every 3 months, such studies can be initiated.

The authors recognize that the relationship between obesity and diabetes is as yet not clearly defined Diabetes has not been produced by overfeeding alone, experimentally or otherwise The nearest approach to this has been the work of Allen[65] who produced symptoms of the disease by fattening partially depancreatized dogs It is possible, or even likely, that the connection between obesity and diabetes is not entirely a causal one and that both reflect some underlying imbalance in the functioning of the body, probably of endocrine origin. Despite this, however, the association of diabetes with a preceding obesity is so close that conditions favoring obesity are undoubtedly related to concomitant variations in the incidence of diabetes

according to their weight when pregnant obese, preobese and normal or underweight, and finally noted whether the weights of the children were

sult showed obese women more often have overweight babies than preobese women and much more often than normal or thin women (2) Whether underweight, normal or overweight, a woman is more likely to have big babies according to her male differentiation Presence or absence of striae have the same evolution as foetal weight and differentiation of the mothers Finally frequency of diabetes in obese women and of those with abnormal G T T is greater when masculine differentiation is greater He relates the

uitary

obesity, and the greater the

The sooner this is realized

[64] Pavel Diabète, 5, 41, 1957
[65] Allen, Stillman and Fitz Loc cit, p 47
[66] Pyke and Plass Jour Endocrin, 15, p XXVI, 1957
[67] Vague Diabète, 6, 267, 1957

by physicians and the laity, the sooner will perhaps the advancing frequency of diabetes be checked. The penalty of taking too much alcohol is well-known, and a drunkard is looked on with pity or contempt and with less sympathy than he deserves. Rarely, persons who become fat deserve pity because of a real tendency to put on weight despite moderate eating, but usually most should be placed in somewhat the same category as the alcohol

ter

pany.[69] If 10 pounds overweight, the average chances of death are increased

weight,

mpany

"The

weight

men was nearly 50 per cent above that expected on the basis of the Standard experience. For chronic diseases of the heart, including coronary artery

Diabetes showed the greatest excess mortality among the major causes, the number of deaths among overweight men being almost 4 times that expected on the basis of Standard experience The most encouraging feature of this study is the finding that weight reduction improves the health outlook for overweight individuals"[70]

Rapid loss of weight by a fat individual, strange to say, may be followed by diabetes How frequently this occurs, we cannot say, but it may be of considerable importance, because we recall several instances, among them Cases 406, 6338, 12570 The fat society woman in her zeal for fashion's lines takes black coffee for breakfast, bouillon and a few green vegetables

fat, low-carbohydrate diet It is true she loses weight but at the expense of lowering her tolerance for carbohydrate Moreover, by this dietetic plan a heavy load of carbohydrate is cast upon pancreas and liver, when the former's insulin-producing capacity has not been trained by previous means to convert it into harmless glycogen, and when the latter's store of glycogen is so low that it functions with difficulty Himsworth's conception of a diet relatively high in fat, predisposing to diabetes is in line with these considerations Moreover, the temporary loss of carbohydrate tolerance

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by

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Minneapolis, Northwestern National

ailable under the title "Overweight

[70] Statistical Bulletin, Met Life Ins Co, 32, No 10, Oct 1951 The mortality comparisons by cause relate to attained ages twenty-five to seventy-four years

[71] Himsworth Proc Roy Soc Med, 29, 731, 1935-6

European breakfast after the long night's fast is safer than our heavier American breakfast. At any rate, after abstinence from food one should

a meal.

Conversely, gain in weight immediately prior to the onset of diabetes is noted frequently in adults. Young[78a] has emphasized this through his article in which the importance of the growth hormone in diabetes is demonstrated with great clarity.

Obesity Explains Peculiarities in Distribution of Incidence of Diabetes.—The preponderant influence of obesity in the development of diabetes explains many peculiarities in the distribution of the incidence of the disease. Thus, in conjugal diabetes I found in a study of 24 couples concerned that there was but 1 of the 27 partners seen by me who was thin Husband and wife alike were fat, and the implication was strong that they contracted the disease from exposure to good food rather than to one another. The frequency of diabetes in the Jewish race has much to do with the obvious obesity which there exists, as stated above. (See page 65.) The increasing affluence of the Jewish race in this country and their readiness to acquire medical knowledge has notably decreased the frequency of obesity among the more prosperous classes One sees much less frequently

muscles is undoubtedly an additional factor So, too, the reputed greater incidence among locomotive engineers who tend to be fat, in contrast to all railroad employees Old statistics showed 1 in 2000 of all trainmen had diabetes, but 1 engineer in 93 Before long data may be obtained from aviators It is pathetic to have them get overweight as they approach middle life Efforts must be accentuated to protect them, as well as policemen and firemen, as they grow older I think Army and Navy personnel realize this, but the professional classes are often oblivious to it So astute

rather than to the infections *per se* Convalescents have big appetites, and unfortunately are almost fanatically overfed during a period of forced inactivity and at the very time when the pancreas must necessarily, like

us at the age of forty-one years, and we can just remember his little spindling legs and delicate frame when he was a boy in the country village

[78a] Young Brit Med Jour, 2, 1167, 1951
[79] Kisch Jour Am Med Assn 64, 1058, 1915

before he attended primary school; many years later he entered a grocery store, "worked like the dickens and ate the same way," until at the age of forty years he was 60 pounds above the average weight, and sugar was found at a life insurance examination

Chronic dietary excesses precede obesity and figure quite prominently in our records as precursors of diabetes. Allen's dogs, artificially predisposed to diabetes by removal of a considerable portion of the pancreas, became diabetic when overfed.

It is, however, the excess of food rather than of available carbohydrate which does the harm. Indeed, a high percentage of carbohydrate in the diet does not appear to predispose to diabetes

Incidence of Diabetes in Very Tall Men.—With evidence pointing more and more strongly each year to the part played by the pituitary in diabetes, the incidence of the disease in very tall men, 6 feet, 2 inches or more, is important. This was investigated by the Metropolitan Life Insurance Company.[73] They found, first of all, that practically there was a normal mortality and a normal pattern of causes of death in this group. Furthermore, school-age children are growing taller and heavier in Michigan and also in the United States as shown by a study of the fifteen-year period ending 1954.[73a]

Incidence of Diabetes and Consumption of Sugar.—An attempt has been made to correlate the increasing incidence of diabetes in this and other countries with the increasing consumption of sugar Statistics, however, do not bear this out, particularly in the United States, where the consumption of sugar has been stationary in recent years, whereas diabetes has increased, and in certain other countries, where the consumption of sugar is high, the incidence of diabetes is relatively low. The consumption of sugar in the United States, as compared with diabetic mortality, is shown in Table 25 However, one must be cautious in the interpretation of the data, because the death-rates are not adjusted for sex, age and other factors Nevertheless it is notable that in the period 1930-1937 the diabetic mortality continued to rise, although the yearly pounds of sugar per capita fell In Australia where in 1937 the per capita consumption of sugar was 121 pounds (55 kilograms) per annum, the diabetic death-rate 16 8 per 100,000, definite efforts were made to discourage its use, not that it was harmful *per se*, but that it destroyed appetite for more wholesome food

Acute dietary excesses are rarely, if ever, associated with the advent of diabetes The incidence of diabetes in the employees of candy factories and candy shops would be of interest in this connection Even yet this question has not been thoroughly investigated The development of diabetes after glucose-tolerance tests has never been reported, or at least brought to our attention.

[73] Dublin and Marks Proc Assn Life Ins Med Directors, 23, 153, 1936
[73a] Statistical Bull Metropolitan Life Insurance Co, 39, Sept, 1 1958

betics prior to the onset of their disease reported diets containing an excessive proportion of fat. It is extremely difficult for diabetic patients even with the best intentions to divorce themselves from their present diabetic diets and to remember and record their previous, non-diabetic diets

Poulsen[75] examined diabetics with varying content of carbohydrate and fat, and constant calorie value in their diet, by Himsworth's technique but failed to confirm his findings. The sensitiveness of resistance to insulin is not constant for each case but dependent among other things on the quantity of carbohydrate and fat in the diet of the preceding period

TABLE 25 —THE CONSUMPTION OF SUGAR IN THE UNITED STATES

Years	*Population Average for Decade*	*Pounds per Capita, Yearly Average*	*Diabetic Death-Rate per 100,000*
1880–1890	55,912,152	44	2 8– 5 5
1890–1900	68,818,801	56	5 5– 9 7
1900–1910	83,275,548	65	9 7–14 9
1910–1920	98,796,383	82	14 9–16 0
1920–1930	114,034,730	100	16 0–19 0
1930–1937	126,222,625	95	19 0–23 7
1938–1948		89	23 9–26 4

Climate.—Climate is closely related with the consumption of carbo-

[illegible]

examined, (2) where the in-

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Public Heal

our belief in

Seasonal Manifestations of Diabetes —Pannhorst and Rieger,[81] reached the conclusion that diabetes cannot be regarded as a seasonal disorder In Massachusetts Lombard[82] found during 1936 and 1937 there were decidedly more deaths in the winter months, December to May, than in June to November, 1779 as contrasted with 1459 The most significant increase was in respiratory diseases, including influenza, 219 versus 94

[74] Himsworth Clinical Science, *2*, 67, 95, 117, 1935, Lancet, *1*, 127, 1936
[75] Poulsen Acta Med Scand [illegible]
[76] Mills [illegible]
Disease, Sp [illegible]
[77] Peters [illegible]
Pt 3, 269 [illegible]
[78] Wilder, Browne and Butt Arch Int Med, 65, 390, 1940
[79] Wilder Clinical Diabetes and Hyperinsulinism, Philadelphia, W B Saunders Company, p 47, 1940
[80] Mills Arch Int Med, *46*, 569, 1930
[81] Pannhorst and Rieger Ztschr f klin Med, *134*, 154 1938
[82] Personal communication from Herbert L Lombard, Director, Division of Adult Hygiene, Department of Public Health, State of Massachusetts

taken for such dates as so to determine with reasonable accuracy the date of onset as contrasted with that of diagnosis.

Example of Multiple Etiology.—Many diabetic patients appear to present multiple causes for their diabetes.

This is well exemplified by the history of a gentleman, aged forty-nine years, Case 954, who consulted us on December 12, 1915. One of his children died in 1901 at the age of two years and another in 1913 at the age of twelve years, both of diabetes. As a child he had measles, scarlet fever and whooping cough, and at twenty-four years was ill for eighteen months with inflammatory rheumatism, and the pericardium was tapped twice. At the age of thirty-four years his weight was 200 pounds, and for his height, 5 feet 11 inches, was 17 per cent above normal. Prior to this time he had indulged in considerable alcohol three evenings a week, and his use of tobacco was more than moderate. He was fond of sweets and occasionally ate ½ pound of candy in an evening During the last two years he took little exercise, and had recently led a strenuous life on account of his active business. An attack of gall stones, which was accompanied by an infection of the biliary tract, led to an operation on November 15, 1915 Prior to the operation the urine was examined and found normal. The anesthetic was ether Convalescence from the operation was satisfactory, but while at the hospital his friends, knowing his fondness for sweets, sent him much candy, which he ate. On December 11, 1915, he observed polyuria, and later he recalled that when nervous and working hard these symptoms had occurred off and on for a day's duration during several years At the same time sugar was demonstrated in the urine, and on the following day when he came for treatment the specific gravity was 1 045 and the percentage of sugar 7.2 The weight of the patient was approximately 185 pounds shortly after the operation, and on December 13 was 177 pounds naked The patient began fasting by omitting his supper on December 12, and the twenty-four-hour quantity of urine, ending December 14, contained only a trace of sugar, and even this was absent the following day Improvement was

Incidence of Diabetes Varies With Chances of Becoming Overweight.—Whatever increases the chances of becoming overweight in those hereditarily predisposed to the disease will tend to bring about a real in-

Thus, in rural communities it is less frequent than in urban communities,

among workers of this type was among the lowest recorded The high diabetes rates in cities, therefore, may be ascribed, in part, to the lighter work done by relatively large numbers of the urban population Improved medical supervision and detection may be the explanation

(*a*) Occupation and Income per Capita —In general, in those countries and cities where the level of *per capita* income is high it is reasonable to assume that the level of nutrition corresponds with *per capita* income. This has been studied carefully by the International Labor Office of the [illegible]

Table 26 —Personal Per Income (Dollars) From All Sources and Incidence of Diabetes, by Region, United States 1929 to 1955

Region	*1929*	*1940*	*1950*	*1955*	*Incidence* of Diabetes 1955*
United States	703	595	1491	1847	15.8
New England	876	757	1628	2087	19.7
Middle Atlantic	979	783	1758	2149	21.5
East North Central	803	667	1661	2078	18.8
West North Central	572	483	1408	1647	16.5
South Atlantic	462	459	1203	1502	12.1
East South Central	348	294	901	1175	10.6
West South Central	436	383	1192	1483	11.5
Mountain	580	516	1389	1663	10.6
Pacific	911	784	1793	2186	10.7

Note Excludes amounts disbursed by the Federal Government to its civilian and military personnel outside continental United States

Source Bureau of the Census, U S Department of Commerce, Statistical Abstract of the United States, 1957, p 303

*Figures show as income lowers incidence of diabetes also lowers, except in Pacific region with highest per capita income and next to lowest incidence of diabetes

(*b*) Increased Use of Power and Machines – The increased use of [illegible]

compared with an increase of 331 per cent in power equipment capacity Despite their lower *per capita* food requirements, workers in industrial and

mercantile countries are able to buy as much food as those in countries where the greater number of inhabitants depend upon more arduous occupations for their livelihood. Consequently, one should expect a great frequency of overweight and, therefore, diabetes, in industrialized and urbanized communities.

(c) INCREASE OF LEISURE.—Another by-product of our mechanized civilization is the increased amount of leisure. Not only do men work less hard during their working hours, but they have more free hours. Fifty years ago the sixty-hour week was general in the United States, Germany, France and Belgium, a fifty-two hour week in England, seventy-two hours in Italy, Russia and other countries. Even longer hours of work were not uncommon. Just before the first World War in many countries the eight-hour day had obtained a strong foot-hold, and it became even more general after the war. Today a week of forty hours or less is the rule.

(d) URBAN AND RURAL.—Whereas in Asia 3 or 4 out of every 5 workers work on the land and produce only a meager per capita supply of food and fiber, in the United States our people are fed and clothed much better with only [illegible] The trend toward the [illegible] energy of large nur[illegible] oval to the city brings about a change to easier work inherent in the differences between the city and country households. Again, transportation facilities and their use are much greater among urban residents. Moreover, the greater availability of concentrated food rich in calories encourages overnutrition among urban residents, so that urbanization is a factor in the increase of diabetes. In 1900, 60 per cent of the people in the United States lived in the country, in 1930, 44 per cent, but in 1950 only 41 per cent were in rural areas and actually on farms 16 per cent.

(e) THE CHANGED POSITION OF WOMEN.—Already this has been discussed under the heading *Sex* (See page 33). The recognition of women has been greater and women have less heavy work to do. In 1956 the percentage of married Americans above the age fourteen was 67 per cent whereas it was only 53 per cent of the population sixty years ago. In the United States women now for the first time outnumber men. The trend is more and more toward a "woman's world."

The major determinant of growth in the population is fertility. Until 1940 there was an almost unbroken decline since 1800. From a depression low of 2.3 million in 1933, the estimated total annual number of births reached an all time high in 1958 of more than 4,000,000. The increase has been most marked among those sectors of population where fertility has been under the most effective control and is normally low – among city families, those living in New England and those with college education. [illegible] As [illegible] ates [illegible] 095, [illegible] 4,719 patients were admitted. To care for [illegible] 600,000 nurses, and 108,973 student nurses.

Upon December 31, 1957,[83] there were 121,000,000 individuals who had voluntary protection with insurance for hospital expenses, 101,325,000 for surgical expenses and 64,891,000 for their regular medical expenses. All of these categories are increasing more rapidly than the general population.

Ingalls, Dickie and Snell[84] have reported a hereditarily obese strain of

and fat. Since the diet selected by the obese animals was suggestive of the restricted carbohydrate diet often prescribed for diabetic patients, quantitative studies of blood sugar were made. It was found that normally fed obese mice had a high blood sugar level, generally above 200 mg. per 100 cc. Non-obese controls had a blood sugar level of the order of 110 mg. per 100 cc.

are insulin-resistant. Even massive doses fatal to normal mice produced no demonstrable toxic symptoms and no fall in blood sugar.

C. THE INCIDENCE OF DIABETES AS INFLUENCED BY VARIOUS FACTORS, ETIOLOGICAL AND OTHERWISE

Incidence Varies With Degree of Interest and Skill Expended in Its Recognition.—"Seek and Ye Shall Find."

Facilities for diagnosis are far greater today and in general in those

this fits in with the incidence of diabetes in urban and rural regions. It is dependent largely upon ... of medical supervision.

Racial Susceptibili ... in Chapter 2, page 41.

Is There a Nervous Element? A strenuous life or a worrying life was

betes temporarily but few cases follow infections. (See Chapter 16). Today infections are far less common and less virulent and of shorter duration because of antibiotics and yet diabetes is more frequent. Von Noorden found a positive Wassermann in 19 per cent of male diabetics and in 6 per

[83] Health Insurance Council: Final Report on Annual Survey, Extent of Voluntary Health Insurance Coverage in the United States as of December 31, 1956, (New York), The Council, 1957.

[84] Ingalls, Dickie and Snell: Jour. Heredit., 41, 317, 1950. Jour. Am. Med. Assn., 147, 4, 328, 1951.

mercantile countries are able to buy as much food as those in countries where the greater number of inhabitants depend upon more arduous occupations for their livelihood. Consequently, one should expect a great frequency of overweight and, therefore, diabetes, in industrialized and urbanized communities.

(c) INCREASE OF LEISURE.—Another by-product of our mechanized civilization is the increased amount of leisure. Not only do men work less hard during their working hours, but they have more free hours. Fifty years ago the sixty-hour week was general in the United States, Germany, France and Belgium, a fifty-two hour week in England, seventy-two hours in Italy, Russia and other countries. Even longer hours of work were not uncommon Just before the first World War in many countries the eight-hour day had obtained a strong foot-hold, and it became even more general after the war. Today a week of forty hours or less is the rule.

(d) URBAN AND RURAL.—*Whereas in Asia 3 or 4 out of every 5 workers* work on the land and produce only a meager per capita supply of food and fiber, in the United States our people are fed and clothed much better with only about one worker in every eight working on farms. The trend toward the cities has resulted in cutting down the expenditure of energy of large numbers of individuals For women, especially, the removal to the city brings about a change to easier work inherent in the differences between the city and country households Again, transportation facilities and their use are much greater among urban residents Moreover, the greater availability of concentrated food rich in calories encourages overnutrition among urban residents, so that urbanization is a factor in the increase of diabetes. In 1900, 60 per cent of the people in the United States lived in the country, in 1930, 44 per cent, but in 1950 only 41 per cent were in rural areas and actually on farms 16 per cent

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(f) MEDICAL SERVICE.—The extent of medical service has increased As of December, 1956, the total number of physicians in the United States was 218,061 The total number of hospitals in the United States was 7,095, and the total bed capacity was 1,607,692 Into General Hospitals 22,089,719 patients were admitted To care for these patients there were 430,000 nurses, and 108,973 student nurses

the prolongation of the interval; (d) that the symptoms and signs of dia- [illegible]

all diabetics

6. This question of trauma as the cause of diabetes should be kept ab- [illegible]

[illegible] reasons the court sitting in judgment [illegible]

which center passed 38,765 soldiers, of whom 12,498 were classified as battle casualties, 2 cases of diabetes and but 1 other was later reported In Germany diabetes in the army was less frequent than in the civil population in which it is universally recognized that diabetes decreased. Yet World [illegible]

when they apply for entrance to college or professional schools and in fact the constant worries to which they are subjected for fear they will fail in their examinations

I have never seen a report that a prisoner condemned to death developed diabetes following the pronouncement of the sentence despite his susceptibility to diabetes by restriction of exercise and abundance of food

The conclusions of writers many years ago and even as late as the last 15 years were honestly arrived at, but I believe the same authors, if today the question of trauma, as a cause of diabetes arose, undoubtedly would reach quite a different opinion These authors did not have the data we have today Thus the influence of tuberculosis and infections in connection with trouble with the pancreas now has largely subsided because tuberculosis causes only 0 2 per cent of the deaths instead of 4 9 per cent in the Naunyn Era or probably 50 per cent in city hospitals at that time and infections 3 4 per cent instead of 13 6 per cent (1922 1936) Syphilis is a rarity So too with heredity, in former days authors cited its absence as an argument that the diabetes resulted *de novo* from trauma Then heredity was

[46] Lommel Med Welt, *13*, 836, 1939
[47] Troell Die Chirurg, *12* 113 1940

cent of females. Our rate in 1940 showed 1.7 per cent as compared with an incidence of 2.7 in the general population.

Arteriosclerosis.—Arteriosclerosis is a bad enough foe of the diabetic without blaming it for the causation of the disease Diabetes is not an old-age disease as proved by the statistics of onset of 9853 of my patients Onset is unusual after 70 years of age. (See page 30) Pathological evidence is against arteriosclerosis as a cause (See page 179). The duration of the diabetes itself is an argument against it, because as a rule, the older the diabetic grows, the less severe the diabetes, and yet the greater the degree of arteriosclerosis

Trauma.—Legal proceedings based upon trauma as a cause of or ag-

United States and in a peculiar sense each one is his "brother's keeper."

Concepts Concerning Trauma and Diabetes.[15]—1. The thesis that trauma *de novo* can cause diabetes has steadily lost support with the expanding knowledge of the nature of the disease. In my 60 years of practice I have not seen a case of diabetes which I believe was caused by trauma. Among the 50,000 patients under our care since 1897, with sugar in the urine, of whom approximately 85 per cent are proved diabetics, I recall no such instance developing among their relatives, although constantly my colleagues and I are seeking to demonstrate an increased heredity in our patients, because we know at the first visit only about 20 per cent show a positive heredity, but after fifteen or twenty years of the disease this may be doubled and in the thirty-year duration cases of diabetes, trebled.

2. Evidence has accumulated to show that trauma indirectly can activate or accelerate, the appearance of a latent diabetes in the hereditarily predisposed, particularly if accompanied by infection, reduced muscular exercise, gain in weight or overeating, but after the subsidence of these factors it reverts to its former latent state

3 Trauma in the course of diabetes has grown in importance, because the average duration of the disease has trebled, thus lengthening the period of exposure Moreover, the danger of exposure to trauma is intensified each successive year a diabetic lives, because time is provided for the disabling complications of the disease to appear and the physical infirmities of the n[illegible]

well said, was put into the grave by World War I, and there it is likely to remain, no data yet appearing to show that it was exhumed during the Second World War.

5 To prove that trauma is the cause of diabetes in any individual case evidence must be at hand to show (a) that the disease did not exist before the trauma; (b) that the trauma was severe, injuring the pancreas; (c) that the symptoms and signs of the disease developed within a reasonable period following the trauma, the etiologic importance of the trauma waning with

[15] Joslin Ann Surg, 117, 607, 1943

the prolongation of the interval; (d) that the symptoms and signs of diabetes were not transitory but permanent, (e) the demonstration of a positive diabetic heredity is always a factor which counts against trauma as a cause, although even without such a history I believe a positive heredity exists in all diabetics.

6. This question of trauma as the cause of diabetes should be kept absolutely distinct from the question of compensation of an individual who is found to have diabetes following an accident Too often, especially in foreign publications (Lommel,[66] Troell[67]) the two are confused, and for social and governmental insurance reasons the court sitting in judgment

he expects a liberal interpretation of social or insurance benefits If trauma

which center passed 38,765 soldiers, of whom 12,498 were classified as battle casualties, 2 cases of diabetes and but 1 other was later reported In Germany diabetes in the army was less frequent than in the civil population in which it is universally recognized that diabetes decreased Yet World

do not bring on diabetes, nor do we know nor have we read in the literature of a surgeon who postponed an operation for fear that the trauma incident to it would cause diabetes Consider the strain thrown upon adolescents when they apply for entrance to college or professional schools and in fact the constant worries to which they are subjected for fear they will fail in their examinations

I have never seen a report that a prisoner condemned to death developed diabetes following the pronouncement of the sentence despite his susceptibility to diabetes by restriction of exercise and abundance of food

The conclusior

15 years were he

the question of

reach quite a di

have today Thus the influence of tuberculosis and infections in connection with trouble with the pancreas now has largely subsided because tuberculosis causes only 0 2 per cent of the deaths instead of 4 9 per cent in the

[66] Lommel Med Welt, *13*, 836, 1939
[67] Troell Die Chirurg, *12*, 113, 1940

demonstrated in 20 per cent of the cases, but a few months ago in 60 per cent of 100 patients whom I personally and successively examined it was present. In January 1957, two patients with a negative heredity appeared on successive days. The first told me that after her 15 years of diabetes that her brother developed it and the other that following her own 17 years of diabetes that diabetes was found in her sister.

One of the last comprehensive [illegible] through its influence on the nerv[illegible] by Sturm.[88] Also, Berning[89] in [illegible] Pankreas-diabetes," cited a case in which diabetes followed in 5 weeks an injury to the skull with subsequent infection in a man without demonstrable diabetic heredity. But again one wonders how many severe injuries and infections near the pituitary have occurred in the past 16 years without diabetes.

In World War I there were 718 admissions for diabetes making a rate of 0.17 per 1000 mean strength. The incidence in World War II, although slightly higher, was slight indeed, ranging from 0.18 in 1944 to 0.34 in 1942. The contrast in death rates is striking. Among the 718 admissions in World War I there were 104 deaths (14.5 per cent mortality), whereas among the 4889 admissions during 1941 through 1944 there were only 50 deaths (1.0 per cent mortality).[90]

So far as the authors can remember, no definite instance in which we considered trauma a cause of diabetes has occurred among the 50,000 patients who have consulted us with diabetes mellitus and glycosuria. We know of no instance in which diabetes has been considered caused by cerebral shock, embolism or thrombosis. We know of no instance in which diabetes has been caused by accidents in the course of college athletics, particularly football, and to fortify our opinion in 1940 we consulted Dr. Arlie Bock of the Department of Hygiene of Harvard University. He wrote "as far as I can determine, no case of diabetes following trauma has occurred among athletes at Harvard. We have had many types of injury but no known injury of the pancreas, and whether such trauma might result in diabetes, I do not know. You know there has been close medical supervision of athletes at Harvard for at least twenty-five years." We know of no instance in which Dr. Harvey Cushing reported diabetes following the development of a tumor in the brain save those instances in which diabetes occurred in connection with acromegaly and basophilism, and 2 patients (out of over 200) with chromophobe adenoma. "What is very significant," according to Dr. Louise Eisenhardt,[91] "is that in Dr. Cushing's own long experience in operating for tumors of the hypophysis or third ventricle he found that such operations did not result in even a transient glycosuria." Dr. Gilbert Horrax writes: "I can certainly confirm what Dr. Eisenhardt has told you regarding pituitary cases, both from my experience with Dr. Cushing's patients and from my own. Furthermore, I have been unable to

[88] Sturm: Deut. med. Wchnschr., 68, 1141, 1942.
[89] Berning: Ibid., 605, 1943.
[90] Marble: Mil. Surg., 105, 357, 1949.
[91] Personal communication.

find in my own records any instance of glycosuria in tumors of the fourth ventricle or fourth ventricle region."[92]

In another personal communication, December 11, 1951, Dr Horrax

who require operation, we have quite a large number who have had only x-ray treatment. In no instance has there been evidence of diabetes in any of the chromophobe pituitary adenomas. There have been perhaps between

Cushing[93] held that the glycosuria of diabetes in acromegaly is due actually to the type of secretion produced by the tumor, and not by pressure of the tumor upon neighboring structures.

States, I have never come across one person who has ever had any symptoms or any knowledge on their part submitted to me by them that they had diabetes or had been suffering from diabetes In all the injuries due to trauma I have never known one injury resulting from trauma that would in any way cause diabetes in any form or any symptoms which would pertain to that disease During my years of experience, 90 per cent of the people who have participated in boxing exhibitions either in the amateur or professional ranks have had repeated examinations and none have ever showed any signs or symptoms of diabetes in any of its forms"

Dr Donald Munro[94] writes "I can cite the fact that in over 3000

article in 1951,[99] reviews the whole question, emphasizing the distinction

194,

[96] Umber Handbuch der gesamten unfallheilkunde, Stuttgart, Ferdinand Enke, vol 1, 1932

[97] Grafe Metabolic Diseases and Their Treatment, Philadelphia, Lea and Febiger, 1933

[98] Ibid Med Klin, 34, 403, 430, 1938

[99] Ibid Lebensversicherung-med, 2, 41, 1950

between the purely traumatic origin of diabetes and the necessity for indemnity or compensation. He points out that for diabetes there is an hereditary tendency of 15 to 55 per cent, and that if one adds endogenous obesity and endocrine diseases to this, one reaches an inborn tendency up to 80 per cent and that therefore in the overwhelming majority of cases there is this congenital functional weakness of the pancreas as the basis of the disease Yet he believes there are exceptions to the rule and he cites the case abstract, p 86. However, in other similar cases of necrosis of the pancreas, with extreme atrophy and destruction of the gland, no diabetes occurred because the pancreas was primarily sound. As for the development after longstanding infections following trauma, it is significant that as a cause of death of diabetics, infections have fallen from 13 6 per cent in 4061 fatal cases, August 7, 1922, to 3 9 per cent in 2909 fatal cases, December 31, 1936.

Professor Grafe has written so extensively and carefully about trauma and diabetes that I asked him for his views at the present time. These are given in the following letter, written January 12, 1958, only four months before his death.

He writes, "Only that individual gets diabetes who, as a rule hereditarily predisposed, is born with insular tissue of inferior value. This pathologic circumstance usually is not enough but needs special factors which play an etiologic role in bringing about the manifestation of the disease. (Compare this with the paper of John of Cleveland mentioned in my article in the Munch Med Wchnschr. 1953) To these belong, besides others, severe traumas of the pancreas, skull and psychological trauma of severest intensity They are certainly rare, but when they bear very close time relationship to the accident, to me it does not seem right just to assume they represent an extraordinary coincidence and especially not to give weight to the opinion of the authority to whom the case has been referred for a decision The examinations of Strieck were confirmed by the experiments of Ransom and Associates with monkeys They also found associated severe pancreatic defects "

[illegible] such as results from a [illegible] the frequency in which [illegible] millions in the country [illegible] would have appeared Furthermore, it must be remembered that it was only one of Ransom's 50 monkeys and none of the 300 cats that showed

[100] Ibid Münch med Wchnschr, 95, 448, 1953
[101] Ibid Deutsch med Wchnschr, 79, 1245, 1954
[102] Ibid In, Handbuch d inn Med, Heraus Mohr und Stachlin, 4te Aufl, Bd 7, T 2, s 110, München, Bergmann, (1954)
[103] Ibid Erhährungs v Stoffwechselkrank 2te Aufl, Berlin, Springer, 1958

diabetes Ransom's summary is as follows. "In nearly 50 monkeys and

Naturally, Young's experiments aroused new interest in the pituitary

pituitaries of 55 of our diabetic patients without finding distinctive lesions

Localized experimental destruction of the hypothalmic region of the

ed

he

Is it surprising that with some 3,000,000 diabetics now alive in this country, and approximately 4,000,000 other individuals whom we can confidently expect to come down with the disease before they die, one may discover glycosuria and even diabetes following the millions of injuries which these people undergo?

Articles by Ramniceanu,[106] Marti,[107] and Mauriac[108] show how tempting it is to assign to trauma the cause of diabetes With the multiplicity of temporary glycosurias found after experiments on the nervous system of

years as possibly a

physical, (2) from

sions with blood in

the cerebrospinal fluid, do not seem convincing If one grants a single one of such cases, one must consider the hundreds and thousands of similar incidents which occur without development of diabetes, and also the possibility that in every diabetic an unnoticed and disregarded accident may have brought on his disease Writers agree that these neurogenic cases are extraordinarily rare and without marked polydipsia, glycosuria and nitrogenous denutrition Although recognizing a lengthening interval between accident and the development of the disease lessons the reliability of an etiological connection, the temptation to argue *post hoc propter hoc* is hard to resist

The older literature upon trauma in relation to diabetes should be discarded, because diagnoses were often inaccurate, due to lack of a test for sugar in the blood and of differentiation of the various kinds of urinary sugar or of renal glycosuria It is notable in the last twenty-one years since the publication of the article on *Trauma and Diabetes Mellitus* in the first

, 1, 1940
04, 232, 1938
119
3, 1948

edition of *Trauma and Disease*[109] how few articles have appeared on the subject and how few cases apparently have come to trial in the courts Reed[110] has reported one such case in detail with appropriate reference to the literature in which it was decided that the injury did not cause the diabetes. Two other similar cases recently have been tried before juries and a similar judgment rendered. Dr. Reed, or the Secretary of the American Diabetes Association can identify these cases to those interested.

The experimental production of diabetes by: (*a*) the injection of an extract of the anterior pituitary into animals, (*b*) the administration of alloxan, (*c*) the production of constant hyperglycemia in cats, are all linked with injury to the islands of Langerhans

In any consideration of trauma and diabetes one should bear in mind that diabetes is universal, that 1 in 59 of the deaths in the country in 1936 was reported due to it, that at autopsy from 2 0 per cent to 3.7 per cent were diabetics, and for females over forty years from 5 per cent to 12 per cent, and that 1 individual in 3 is a probable carrier of the disease. These facts are all important when the question of trauma arises, because they indicate how widespread the disease is and, therefore, the necessity of knowing whether the individual in question already had the disease before the accident

The diagnosis of the diabetes must rest upon a sure foundation The sugar in the urine must be glucose, not levulose or pentose, and be dis-

conditions often prevail

The investigation of any case of trauma as a possible factor in the causation of diabetes leads to a study of the family history of the patient for heredity, past or present overweight of the patient, and in children overheight, the presence of an infection, circumstances which might have prevented use of the muscles, because these states are favoring influences

and followed by a long period of unconsciousness and marked abdominal pains, was found to have diabetes, by adding that subsequently the son developed true diabetes He therefore concludes that one must exclude a traumatic origin of diabetes in this case

Trauma is practically never the primary cause of diabetes Like von Noorden,[112] Umber[113] and Labbé,[114] we believe that it is only under extraordinary conditions that it can directly cause the disease

by Brahdy and Kahn,

Thieme, p 32, 1930

With this view Viggo Thomsen agrees and in a personal letter in 1958, reaffirms his original view,[115] basing his opinion upon studies of blood and urine of 144 patients at the time of and subsequent to accidents, upon the absence of any essential difference in the frequency of diabetes in injured and non-injured persons in the Aarhus Hospital in Denmark between 1921 and 1935, upon a critical review of 81 cases reported in the literature as

destructive that it is almost inconceivable that it could be compatible with life Among the more than 27,000 cases of diabetes seen by von Noorden, the 7,000 treated by Umber since 1923 and the 50,000 patients who have consulted us for sugar in the urine, there has been no patient whose diabetes they or we believe was directly caused by trauma. It is true that various authors, but with less experience, particularly in years gone by, thought and do still believe otherwise Von Noorden in his early life, and the senior author, too, suspected that trauma was a feature, but the more we both saw of diabetes the less likely did either of us believe it to be a cause of diabetes directly or indirectly On the other hand, it is recognized that frequently immediately following trauma an existing diabetes becomes apparent and exceptionally that the trauma indirectly may activate a

severe trauma may, but not necessarily, make a diabetes more severe. R Herbst[117] also expresses views in line with those of the authors

A special study was made of the possible influence of trauma in 2283 diabetics in Lodz, Poland, by Lisiecka-Adamska and Grott[118] Emotional trauma was noted in 4, injuries of the skull in 20, in other regions of the

physical examination by the method of Grott, paying special attention to

demonstration of the methods used and described at various times by Professor Grott

in

dis

disease earlier in life if he were fat, subjected to an infection, particularly

[115] Thomsen Studies of Trauma and Carbohydrate Metabolism with Special Reference to the Existence of Traumatic Diabetes, Acta med Scandin, Suppl *91*, 1938 See also Editorial, Jour Am Med Assn *112*, 1952, 1939

[116] Grote Deutsche med Wchnschr, 57, 984, 1931

[117] Herbst Münch med Wchnschr, *11*, 1262, 1936.

[118] Lisiecka-Adamska and Grott Diabète, *6*, 28, 1958

in the region of the biliary tract, was incapacitated to such an extent that he could not use his muscles normally, or acquired a permanent lesion of the pituitary, thyroid, adrenal glands, or liver, but not as a result of mental or emotional strain. Suppose a man is born with a diabetic tendency, escapes the disease in childhood, but when he comes of age realizes the tendency exists and in consequence tries to avert the development of dia-
...event the onset
... the same, util-
... disease of the
endocrine glands or the liver. If this man has an accident which interferes

tolerance test have disclosed it? Furthermore, would not the same answer hold if by chance or environment, rather than by design, all these precautionary measures against the onset of diabetes had been fulfilled?

If one should grant that diabetes developed prematurely in a predisposed individual, what effect would it have upon him? Above all else it would mean health *versus* chronic illness and his expectancy for life would be shortened. How much this would be is not certain, but it has been calculated by the Statistical Department of the Metropolitan Life Insurance Company, based upon death rates of our patients, subsequent to first observation, regardless of duration of diabetes. Thus a diabetic boy of 10 years has an expectancy of 43.6 years compared with 59 years for the ordinary child and a diabetic girl 45 years compared with 64.3 years, and a diabetic at 60 years an expectancy of 10.6 years instead of the ordinary expectancy of 15.8 years. See Table 40. These calculations were based on the death rates of our patients in 1947–1951.

The situation alters materially, however, when one compares the effect of an injury upon a diabetic and a non-diabetic. Here the effect of the injury must be calculated upon the diabetic's previous life expectancy and not from that of the total population.

toes and here trauma is an important factor. Trauma in the course of diabetes is destined to become increasingly important because diabetics are living so much longer and thus the time-risk of exposure is about

coma or insulin reactions. All of these states in and of themselves constitute

hazards which he must face and because he has these he is less able to protect himself from trauma

The manifold opportunities for trauma in the course of insulin reactions and the medico-legal complications which may ensue have been enumerated by Adlersberg and Dolger.[119] The picture which they paint is far more vivid and the frequency of the instances cited appears far more common than we meet in our practice

Direct Trauma.—The pancreas is so deeply situated in the abdomen, so well protected posteriorly by the backbone and the strong muscles of the back, and anteriorly by the stomach, intestines, the liver, and the overhanging chest wall, that it is sheltered from all save the severest injuries and almost absolutely excluded from selective and independent injury The causation of diabetes directly by trauma, therefore, can only take place when the pancreas is injured to an extraordinary degree To bring this about it is only conceivable when the injury is violent, productive of immediate symptoms of grave intensity accompanied by excruciating pain, and involves other surrounding vital structures of the body with prompt [illegible]

to cause diabetes

To produce diabetes trauma must interfere with the secretion of the islands of Langerhans of the pancreas, but that it can do this except by actual physical injury to the same is not known We know that the secretion of insulin is controlled chiefly if not wholly by the amount of sugar in the blood and that the blood sugar in turn is influenced by nervous stimuli originating in the sympathetic nerve tracts, connecting adrenal, thyroid, [illegible]

chiefly rests upon an experimental basis of an intricate nature It is largely a question as to how much the liver enters into the problem Recently even the interpretation of the Claude Bernard puncture is questioned

Young's demonstration of the production of diabetes in dogs by the injection of an extract of the anterior portion of the pituitary gland suggested at first an extra-pancreatic influence, but the later finding of disease of the islands of Langerhans showed the pancreas was concerned with its development and thus maintained the unity of the disease This also holds true for alloxan diabetes

There are few cases of diabetes in the literature attributed to direct trauma which rest on as good a foundation as that reported by H Gideon Wells[120] of Chicago However, the diagnosis in his case depends upon one examination of the urine obtained after death, and Thomsen excludes it Another case which we were privileged through the kindness of Professor

[119] Adlersberg and Dolger Ann Int Med, *12*, 1804, 1939
[120] Wells Am Jour Med Sci, *164*, 479, 1922

Grafe of Wurzburg to report for the first time is more complete, although even with this patient the urine had not been tested for some time prior to the accident

[illegible]

abdomen and chest were pressed against the steering wheel, but he had no pain following the accident and felt well The automobile was righted and he resumed driving, but developed what was diagnosed as a gall stone attack in three hours, yet he continued the journey with a hired chauffeur on May 20. The attack per-

[illegible]

A second case is reported by Stern[121] to whom we are indebted for subsequent information regarding the patient

The patient was hit in the left side and back by an automobile August 12, 1926, suffered with severe back pain in the abdomen for six days, and when about to leave the hospital on the eighth day went into severe shock and collapsed with agonizing pain in the abdomen Laparotomy revealed a hemorrhagic pancreatitis

[illegible]

A third case, subsequently recalled by Grafe,[122] from his days as a medical assistant, deserves mention, because of the presence of diabetes for a year or more after injury to the pancreas, with later recovery following subsidence of the suppurative pancreatitis The case is as follows.

Case 143 —A man with a severe gunshot wound of the pancreas had a suppurative pancreatic fistula for a year A severe diabetes developed, which lasted for

[121] Stern Am Jour Surg , 8, 58, 1930
[122] Grafe Med Klin , 34, 403, 1938, 34, 430, 1938

[illegible]

creas, provided, as Allen in his beautiful experiment showed, excessive carbohydrate alimentation is not administered. In favor of this explanation is the recovery from the diabetes as a result of the healing of the suppuration with closure of the fistula.

Geiger and Benson[123] and Lommel[124] have reported cases in which they believe the possibility of trauma having caused the diabetes should not be ignored. They concede the difficulty in reaching a decision, yet plead for an open-minded consideration of the facts even though scientific reasoning points against a traumatic etiology of the disease. Troell,[125] in Stockholm in a carefully prepared article, reports 10 cases in which glycosuria or diabetes was present with trauma, and even passed upon by the board of reparations In only 2 of these was the trauma considered as a cause of the diabetes The evidence by no means was as strong as in Grafe's case and, in one, followed an injury to the elbow, and the *post hoc propter hoc* argument was raised because the urine was said to be sugar free the day before the accident These cases are carefully reported and the circumstances of each are clearly discussed Troell, like Lommel, is unwilling to concede that trauma to the pancreas alone can cause diabetes His [illegible]

he claimed had led to infection, and the injury had resulted in diabetes [illegible]

fully that this accident had caused not only the injury to the toe, but *via* [illegible]

In general the shorter the interval between the occurrence of the trauma and its alleged effect, the greater the likelihood of a relation between the two Each day which passes without diabetic symptoms or accentuation of diabetic symptoms lessens the probability or even the possibility of [illegible]

[illegible]

[123] Geiger and Benson Am Jour Surg, 47, 672, 1940
[124] Lommel Med Welt, 13, 836, 1939
[125] Troëll Loc cit, p 77.

similar to those of Davidson and Allen,[126] who performed sugar tolerance tests upon patients with concussion of the brain and skull fractures. Mock and deTakats[127] believe a head injury, if there is a diabetic tendency, may become a serious menace. Dr. deTakats wrties as of March 18, 1946: "The conclusion reached in the study of head injuries which was undertaken with Dr. Harry Mock was that a temporary hyperglycemia occured after any cerebral anoxia However, we did not encounter a single case in which diabetes appeared after a head injury in a patient in whom there was no suspicion of a latent diabetes beforehand. . . . Since that time I have had very little contact with traumatic and industrial cases, but it has been the impression of our group that a latent or clinically not manifest diabetes might become more severe after head injury. I recollect one case of a known diabetic with a fasting blood sugar of 140 milligrams per cent who was sugar free without insulin This rather obese woman developed a rather severe acute exacerbation of her diabetes. Six weeks later, however, her diabetic status was identical with what she had before the head injury." Dr. deTakats[128] adds in 1951, "Recent knowledge concerning the phenomenon of stress and the pituitary-corticoadrenal response of the body to a variety of insults places the so-called "traumatic diabetes" which is *temporary* and *insulin-resistant* in the category of ACTH diabetes which occurs after fractures or extensive burns or any major insult Whether the use of hypertonic glucose or sucrose to combat cerebral edema, which was in use years ago in cases of head injury, aggravates this ACTH diabetes is not known but quite possible "

Compare Cushing, Eisenhardt and Horrax, see page 79, also Thomsen, page 83

Indirect Trauma —Indirectly trauma might cause diabetes if it could set in motion processes which would lead to the destruction of a sufficient number of the islands of Langerhans of the pancreas One-tenth of the pancreas may suffice to prevent diabetes, but usually does not do so, so that we can say that diabetes will occur only when more than five-sixths, more probably *nine-tenths, of the islands of Langerhans are destroyed* or rendered inactive This seldom happens as a result of disease, despite the comparative frequency of pancreatitis and of cancer of the pancreas

For experimental pituitary diabetes, see page 125, and for alloxan diabetes, see page 132

An infection makes diabetes worse Could it bring on diabetes through involvement of the pancreas? In the opinion of our group infections are

[126] Davidson and Allen Bull, Johns Hopkins Hosp , *37*, 217, 1925
[127] Mock and deTakats Ann Surg , *90*, 190, 1929
[128] Personal communication
[129] Lande Klin Wchnschr , *101*, 350, 1931

patient stay sugar-free upon a diet with 200 grams of carbohydrate The diabetes may subside so completely after convalescence from the carbuncle that it is believed by the unwary to have been temporary.

e examination in

but (1) he had a

which the onset

of diabetes is frequent, (3) by being above normal weight, he was three

Occasionally an infection apparently of trifling nature in a diabetic may lead to dire, even fatal, consequences This happened when a patient pulled out a protruding hair from the nose, and in another instance as a result of a simple paronychia. Very commonly trifling injuries to the feet

Already we have summed up the prevailing view regarding the influence of the nervous system, physically or psychically, in the etiology of diabetes or upon its course, but we will cite a few examples

which diabetes appeared to have arisen as a sequel to an extraordinary, physical trauma Diabetic symptoms, polydipsia, polyuria, physical and mental depression

[150] Dublin, Jimenis and Marks Proc Assn Life Ins Med Directors, *21*, 34, 1934
[151] Rarely the symptoms of diabetes may follow a nervous shock as in an obese Italian, described by Root, but who can accept an etiologic relation, when the vast majority of cases begin without such shock? Root Med Clin No Am, *21*, 441, 1937

In contrast is cited Case 13332 who was in perfect health so far as he or his family knew on December 24, 1934. That night this fourteen-year old Jewish boy, with

re was no
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He was

known at
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our auto-
re reason
reaction
f his dia-

There are approximately 30,000 (one per cent of 3,000,000) diabetics in the United States with the history of a sudden onset of diabetes. What opportunities they afford for traumatic, diabetic exploitation! This special group represents the *elite* corps from which recruits for the traumatic etiology of diabetes should be most easily obtained, but that we have recognized none with a traumatic basis among these we have personally studied, is of some import.

Our skepticism concerning the etiological significance of organic or functional brain disturbance as a forerunner of diabetes is shared by von Noorden and Umber and many others, but another group takes a different view. Among these is Schur[133] who cites Umber's notable case.

fear of
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is sleep
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Injuries to the head quite frequently lead to glycosuria, but this is temporary in character They are more prone to do this if there is a concussion as well It is tempting at times to say diabetes results, but as yet I have not been satisfied to accept such an interpretation Only too rarely is the case history as complete as that reported by Langer [134]

A different point of view is brought out by the studies of Gissel [135] Gissel observed hyperglycemia up to 270 milligrams per cent in all head

[132] Carrasco-Formiguera In Spanish edition of Joslin's Treatment of Diabetes Mellitus, Barcelona, Montaner and Simon, p 141, 1925

[133] Schur Ztschr f klin Med , *123*, 800, 1933

[134] Langer Monatschr f Unfallheilkunde, No 1 S 2, 1896

[135] Gissel Chirurg H , *1*, 5, 6, 1933

injuries resulting in unconsciousness in the first three to four days after the

opinion, who quotes Gissel, indicated that a transitory injury to the function of the pancreas can occur. Isaac, therefore, believes that in rare cases injuries to the skull can reveal diabetes or set it loose, provided the constitutional tendency is present. How this is brought about he does not pretend to say, but he agrees with Stern,[137] Grote,[138] and Jacobi and Meythaler[139] that just because we cannot completely explain the anatomical connection between the brain and pancreas is no reason to say it does not exist and thus totally discard traumatic diabetes. Grafe wrote in 1938, "The cerebral production of pure diabetes up until now has succeeded neither in our hands nor in those of others, but must be set down on the whole as possible or even probable." For his present opinion see his letter of 1938, on page 80. The work of Young does introduce a pituitary element, which, however, it should be easy to exclude by the absence of direct

blood sugar. Timpe[141] investigated 300 fresh fractures on the first, second, fourth and seventh days. In only one case was there found a condition relating to diabetes.

Fractures are common in diabetic patients. It is the rule for the bone to heal promptly, and we recall but one instance in which this has not taken place, Case 14335, female, aged sixty-eight years, duration eight years, who sustained a broken hip which failed to unite despite many operative attempts. Now that diabetics live longer, there is more opportunity for fractures to occur, and we expect the incidence of fractures will show a

Possibly this will not be noted much in the future, and writing in 1938, instances seem less comon than in former years. These occurred as spontaneous or nearly spontaneous fractures of the spine. In these cases the vertebræ showed deficient calcium. It is easy to understand that this could take place formerly when milk was so largely exlcuded from the diet and

[136] Isaac. Monatschr. f. Unfallheilkunde, *40*, 181, 1933.
[137] Stern. Traumatische Entstehunginnerer Krankheiten, 3te Auf., Jena, Gustav Fisher, 1930.
[138] Grote. Loc. cit., p. 83.
[139] Jacobi and Meythaler. Ergebn. d. inn. Med. u. Kindheilkunde, *45*, 189, 1933.
[140] Konjetzny and Weiland. Mitt. a. d. Grenzgeb. d. Med. u. Chir., *28*, 860, 1915.
[141] Timpe. Arch. f. Orthopäd. u. Unfall. Chir., *35*, 112, 1935.

thus the main source of calcium removed. Likewise, formerly, there was more acidosis than today, and this would tend to remove calcium. A succession of fractures is not so very rare. Case 13906, onset of diabetes mellitus at 34 3 years, has sustained 7 fractures in the course of seven years.

Although the pituitary, thyroid and adrenal glands are intimately associated with the pancreas, experimental traumatic injury or disease of the same does not cause true diabetes. This statement still holds despite the work of Houssay and Young and Best on the pituitary and that of Long and Lukens and also Ingle upon the adrenal.

Trauma in Connection with the Use of Insulin.—Within a very few months after the use of insulin in human beings, instances of infection at the site of injection of insulin practically ceased. Among 1838 admissions to the George F Baker Clinic during 1941 there were but 8 who entered for abscesses due to the injection of insulin. Needles broken in the skin during injections have never led to serious trouble in our experience. A far more frequent, and infinitely more serious, opportunity for trauma is that incident to an insulin reaction. However, despite the thousands of insulin [illegible]

neurologic patients. [illegible] result from the patien[illegible] plugged the trachea [illegible] reaction has been mistaken for diabetic coma and, in consequence, a dose of insulin has been given which resulted in death. Fortunately, such instances are few. See Joslin's articles in *Trauma and Disease*,[142] *Annals of Surgery*[143] and Stern[144] in which the older literature is reviewed

Murder due to insulin poisoning has recently been reported. A study of this case reveals the keen detective work and the cooperation of many laboratories.[144a]

An editorial in DIABETES cites references hitherto not mentioned by us.[144b] These papers emphasize how little actually is known about the etiology of diabetes They present possible rather than convincing facts.

What has been the effect of the mine disaster at Spring Hill, Nova Scotia, on the miners and their families? Will the resulting incidence of diabetes there differ from that in a similar community not exposed to stress, as in Oxford, Massachusetts, investigated by Wilkerson and Krall? Do convicts condemned to death develop diabetes?

Liver.—(See pages 154–155 and Chapter 17)

Various Endocrine Glands.—The influence of the endocrine glands is discussed on pages 124–129 and also in Chapter 26

Gout.—The number of cases of gout occurring in association with

[142] Joslin In, Brahdy and Kahn Trauma and Disease, 2nd ed, Philadelphia, [illegible]

[illegible] med Wchnschr, *106*, 859, 1956, Glatzel [illegible] Practitioner, *178*, 590, 1957, Levitt New [illegible] Münch med Wchnschr, *98*, 1421, 1956

diabetes among our clientèle is trifling. However, even a single case is important, because in one instance under our care a bursa, which later ... hereas with the

proximately twice the expected incidence of diabetes in reported control

School of Medicine[144c], of 143 patients with gout 28 per cent showed elevations in blood sugar and the authors conclude the incidence was 50 per cent greater than in a non-gouty control population.

D THE CLINICAL PREVENTION OF DIABETES

The slow and prolonged onset of diabetes should be utilized for its early

monly as those with little or no glycosuria By testing the urine alone, one-half of the unknown cases were found Particularly should one seek

diabetic heredity in 1000 cases but points out it is still more important to study

more

investi

of rev

bility that pancreatitis in the course of infections may be a factor in the development of diabetes even though the interval may be many years It is refreshing to read his article because it is stimulating, and looks at the subject from a different point of view However, recently I personally interrogated most carefully 100 successive cases and the heredity was 60 per cent This is a figure which now I find in practically all groups in which

[144b] Ishmael Jour Oklahoma Med Assn, 38, 415, 1945
[144c] Weiss *et al* Metabolism, 6, 103, 1957
[145] Wilkerson and Krall Loc cit p 19
[146] John Ann Int Med, 8, 198, 1934
[147] Blotner Loc cit p 48
[148] Boulin Traitement du Diabète Sucré, Paris, G Doin, 1956

the social status of the patients is of such a character that they know the cause of death of their ancestors.

Diabetes in our opinion is 100 per cent hereditary. Therefore, the founda-

one in three of the population in the United States probably has a diabetic predisposition. Yet at the first visit of a new patient one should allude to the seriousness of its propagation. If the patient is a parent, it is important to test all the decendents and, if a child, all the ancesters because so often diabetes appears in the child long before it has been recognized in older relatives. Boulin reports one instance in which the mother was found to have diabetes 51 years after its appearance in the child. In fact, seek for diabetes in all the relatives of a diabetic. Indeed, one can predict that 90 per cent of the mothers will develop diabetes whose child at birth weighs

Diabetics who died in the Naunyn Era (1897–1914) lived 4.9 years as compared with 18 years for fatals in 1956 and 1957. The true duration of life of all diabetics seen in that early period has now been computed and

betes is obesity. One need not hesitate to preach against it in season and out of season because it is harmful not only in diabetes but in circulatory diseases. Obesity precedes diabetes in 85 per cent of the cases. Under no circumstances should a diabetic or the relative of a diabetic be fat. The danger of overweight can be driven home in all sorts of ways. Thus, 10 pounds overweight on the average increases the chances of death by 8 per cent, 30 pounds by 28 per cent, 50 pounds by 56 per cent and 80 pounds overweight by 116 per cent[151]. An attempt should always be made for the correction of overweight where it exists.

out for life.

Tests for the discovery of the disease among the relatives of diabetics should be made less costly. It should be publicized in all communities that at certain times or places individuals can secure such tests for diagnosis or treatment at minimal expense, just as one can secure a free chest x-ray. So important is the detection of the disease in an early stage that I expect glucose tolerance and even provocative glucose tolerance tests will be employed more and more in the near future. Today, one never treats a dis-

[149] Hoet. Diabetes, 3, 1, 1954.
[150] Kriss and Futcher. Jour. Clin. Endocrinol., 8, 380, 1948.
[151] Fat Can Be Fatal. Loc. cit. p. 68.

betic patient as an isolated diabetic, but tries to protect the entire family just as one would if there was an epidemic of diphtheria or typhoid fever; indeed, the situations are similar in many respects

Surgery should be invoked to remedy the predisposition to diabetes.

One

I saw

diabet

of the possibility of diabetes and thereupon took such prophylactic care of themselves that they are in excellent health. These patients are almost as

students, nurses and doctors as I can because I know the example of one such case counts far more than any words of mine

With Boulin, let us stop saying that diabetes is irreversible and that the doctor has arrived too late

E. INSURANCE

Most insurance companies insure diabetics Naturally the costs are greater because the mortality of diabetics is higher. See Table 40 for a comparison of death rates of diabetics with non-diabetics at different ages, and Table 44 for expectations of life

A recent survey by J E K Kennedy[151a] showed an acceptance ratio of 75 per cent Today almost any kind of insurance may be obtained by diabetics and would be much cheaper if they took better care of themselves. Indeed the patients themselves largely control the situation.

For diabetics, it is obvious that an extra premium must be charged Physical findings such as overweight, abnormal electrocardiogram and increased blood pressure are important Some companies consider the duration of the diabetes and the age at its onset of considerable significance However, by far the most important factors are the care and supervision given the diabetic by his doctor and by himself

Dr R C Montgomery[152] in "The Truth About Life Insurance for Diabetics" writes "From the insurance company's point of view the average diabetic prospect (1) Is between the ages of 20 and 70 years (Some

not more than 75 units of insulin per day.

The reason for declining the applications received from diabetics are one or more of the following: (1) Lack of supervision and control (2) Ab-

[151a] Kennedy Diabetes, 7, 320, 1958
[152] Montgomery A D A Forecast, 10, 1, 1957
[153] Shepard and Marks Minnesota Med, 38, 736, 1955

7

the social status of the patients is of such a character that they know the cause of death of their ancestors.

Diabetes in our opinion is 100 per cent hereditary. Therefore, the foundation stone for [illegible] by individual [illegible] marry one ano [illegible] one in three of the population in the United States probably has a diabetic predisposition. Yet at the first visit of a new patient one should allude to the seriousness of its propagation. If the patient is a parent, it is important to test all the decendents and, if a child, all the ancesters because so often diabetes appears in the child long before it has been recognized in older relatives. Boulin reports one instance in which the mother was found to have diabetes 51 years after its appearance in the child. In fact, seek for diabetes in all the relatives of a diabetic. Indeed, one can predict that 90 per cent of the mothers will develop diabetes whose child at birth weighs 6000 grams, 13 pounds,[149] and 100 per cent if 14 pounds.[150] The pregnant woman should be checked not only during her pregnancy but for life because diabetes is more common in those women who have borne children.

Diabetics who died in the Naunyn Era (1897–1914) lived 4.9 years as compared with 18 years for fatals in 1956 and 1957. The true duration of [illegible]

[illegible] circumstances should a diabetic or the relative of a diabetic be fat. The danger of overweight can be driven home in all sorts of ways. Thus, 10 pounds overweight on the average increases the chances of death by 8 per cent, 30 pounds by 28 per cent, 50 pounds by 56 per cent and 80 pounds overweight by 116 per cent[151]. An attempt should always be made for the correction of overweight where it exists. [illegible]

[illegible] of controlling the disease at its inception and thereby assuring the protection of the patient. However, control should not stop here, but be carried out for life.

Tests for the discovery of the disease among the relatives of diabetics should be made less costly. It should be publicized in all communities that [illegible]

[illegible] glucose tolerance and even provocative glucose tolerance tests will be employed more and more in the near future. Today, one never treats a di-

[149] Hoet. Diabetes, 3, 1, 1954.
[150] Kriss and Futcher. Jour. Clin. Endocrinol., 8, 380, 1948.
[151] Fat Can Be Fatal. Loc. cit. p. 68.

If such persons would limit their families to one child or even two, the same result would be accomplished, since for a family to survive the number of children in each generation must exceed three." In Dr. Priscilla White's series of 1700 pregnancies in diabetes there have been 12 instances of 4

2000 years

Diabetics like non-diabetics are susceptible to other diseases and obviously complete physical examinations of both individuals contemplating marriage should be carried through and the results of those examinations made known. Especially is this important because certain diabetic complications are so serious that of themselves they preclude marriage. Such are active tuberculosis, complications in the eyes, heart and blood vessels, the kidneys, loss of potency and bronze diabetes.

whether the diabetic has, or at least, is eligible for insurance.

For further discussions appropriate to the marriage of diabetics see: prevention of diabetes, p. 59, heredity, p. 50, and pregnancy, p. 59.

G. EMPLOYMENT OF DIABETICS

If diabetics control their disease, are absent on sick leave less than the rank and file of non-diabetics, and do their work better, there will be plenty of opportunity for them to get work.

The United States Civil Service Commission is liberal in its recommendation for employing diabetics. In fact, approximately 1,000 jobs are available to diabetics. The Commission's viewpoint is well shown by the following paragraphs.[155]

"The U. S. Civil Service Commission believes that persons with controlled

maintained."

"Prior to 1941, persons who were known to have diabetes mellitus were not acceptable for Federal employment. Since that time physical standards have been modified to permit the acceptance of persons with the condition, providing they are able to perform the duties of their positions efficiently

[155] Employment of Diabetics in the Federal Service, CSC Form 533, Oct., 1956.

normal conditions of the heart and blood vessels. (3) Kidney disorders (4) High insulin dosage. (5) Alcoholic habits. (6) Too recent diagnosis of diabetes, so that complete information about its control cannot yet be obtained. (7) Overweight (8) Visual disturbances. (9) Age.

The largest single reason for refusal of companies to issue insurance is "lack of supervision and diabetic control."

The use of alcohol, it is felt, is not advisable for the diabetic, since it can disturb the food-exercise-insulin balance that the doctor has arranged. [illegible]

enforced

To summarize: As a result of modern statistical research, life insurance is now available to many diabetics. The amount of extra premium to a

It

The

dia-

betes—diet, taking his insulin, testing his urine and seeing his doctor at reasonable intervals

F. MARRIAGE

It is a great advantage for a diabetic to be married because of the intimate *protection and care thereby attained. However, it is only fair that the* non-diabetic partner should realize that the average diabetic has one-fourth to one-third less life expectancy than the non-diabetic, that the shorter the existing duration of the diabetes the better the chance for children, and that strict control of the diabetes is the best provision for freedom from complications and for a long life Also, one should mention that there is a somewhat greater incidence of abnormalities in the children of diabetics. A thorough understanding of the disease by the non-diabetic partner is essential Those contemplating matrimony should get acquainted with other couples and other diabetics I do not recall any divorce to have taken place when a nurse, knowing what the disease is, has married a diabetic and

those with a slight hereditary tendency to it because this would involve about one-third of the population of the country and that third which belongs to the class brought up under the more favorable surroundings

Wilder[154] writes, "It is not necessary to demand 'mass sterilization' or even to ask that members of diabetic families voluntarily remain childless

[154] Wilder P 54, Loc. cit. p. 71.

Chapter 4

PHYSIOLOGY OF DIABETES MELLITUS

ALBERT E. RENOLD, M.D.

A. INTRODUCTION

THE evident metabolic nature of the functional disorder underlying diabetes mellitus is responsible for the unique place which this human disease has occupied for at least two centuries in the mind not only of

mellitus, diabetes "sweet as honey." Since that time interest in diabetes mellitus has repeatedly provided an important and at times the only meet-

biology and biochemistry, the latter being in turn the necessary basis for

Allen, Stillman and Fitz.[1] Here it will suffice to state that although the symptoms of diabetes were noted by ancient writers and the name "diabetes" given at the beginning of the Christian era, it was not until early in the sixteenth century that Paracelsus evaporated the urine of a diabetic individual and found a sizable residue which he mistook for salt. A century and a half later Thomas Willis recorded the sweet taste of diabetic urine and in 1775, Dobson brought out the fact that the sweetness of the urine was due to sugar. In the middle of the nineteenth century Claude Bernard made his notable contributions. He was the first to determine with reasonable accuracy the percentage of sugar in the blood. He discovered glycogen and the glycogenic function of the liver. He founded the theory of the formation of sugar from protein. He produced glycosuria by puncture of the floor of the fourth ventricle. In 1869, Langerhans described the islet

[1] Allen, Stillman and Fitz. Total Dietary Regulation in the Treatment of Diabetes, New York, Rockefeller Institute for Medical Research, Monograph No. 11, 1919.

based upon: whether the condition is under proper control; whether there is a history or existence of complications which would render the person a poor risk in the job under consideration; history of attacks or insulin reactions, and whether the individual receives regular, periodic urinalyses and blood sugar tests."

"Diabetics should work the same hours on a steady shift and should not be subjected to *irregular* heavy physical demands to the extent that a controlled regime is precluded."

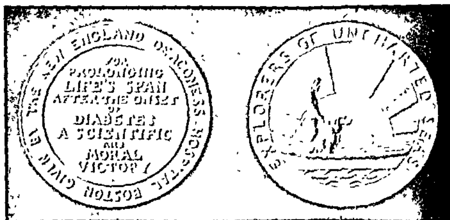
"Diabetics should carry cards or tags at all times identifying their condition."

"Diabetics should be under the guidance of their clinic or personal physician and should report periodically for physical examination and medical evaluation."[136]

From the above, it is apparent that the employment of diabetics in the future largely depends upon the behavior of the diabetics themselves.

Might one not utilize insurance companies for intensive efforts toward early detection of diabetes. They could require that yearly examinations of the urine be reported.

Costs of blood sugars are far too high. Special inducements should be offered, using wholesale methods which would encourage patients to come before 9 A.M., or at some special hour or on a special day when the rates would be lowered.



AT THE GEORGE F. BAKER CLINIC
NEW ENGLAND DEACONESS HOSPITAL
A MEDAL DESIGNED BY AMELIA PEABODY IS GIVEN
TO THOSE WHO HAVE CONQUERED DIABETES
BY LIVING LONGER WITH IT
THAN THEY WERE EXPECTED TO LIVE WITHOUT IT

[136] Report of the Committee on Employment of the American Diabetes Association, Revised May, 1957. Diabetes, 6, 550, 1957.

and initiation of its catabolism may exceed the metabolic potential of the tissues to oxidize them completely. Under these conditions intermediary products of fat and protein catabolism, particularly ketone bodies may accumulate and lead to ketosis Ketosis is accompanied by ketonuria and since the ketone bodies are primarily acids (acetoacetic acid and beta hydroxybutyric acid), cations accompany their urinary excretion When this accumulation of ketone bodies becomes excessive ketoacidosis and, by as yet unclear mechanisms, coma and death result.

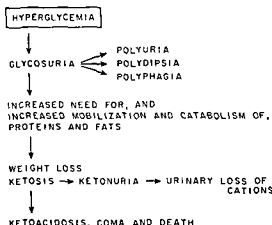


Fig. 5

It should be clearly u[illegible]
the preceding sequence
hypothetical and that,
causation of the hyper
mentally and clinically, the acute diabetic syndrome may be incomplete and may be limited to hyperglycemia alone or include a few but not all of the additional steps described in Figure 5 This is usually thought to represent a quantitative rather than a qualitative difference The presence of persistent hyperglycemia is usually taken to indicate the presence of at least a partial acute diabetic syndrome.

C THE MAJOR ENDOCRINE DEFECT IN DIABETES MELLITUS

It is useful to distinguish betw[illegible]

a state of affairs for which observations on the production of *experimental*

cell formations in the pancreas which bear his name, and twenty years later von Mering and Minkowski demonstrated that the removal of the pancreas in dogs causes diabetes. In 1921, the active, blood glucose lowering principle of the pancreatic islets was isolated by Banting and Best and in 1922, it was made available for the treatment of patients. These are but the highlights, many other workers contributed important facts, particularly since the middle of the nineteenth century. Indeed, prior to the discovery of insulin in 1921, by Banting and Best, others had even achieved a certain degree of success in the preparation of pancreatic extracts.

The discovery of insulin in 1921, has introduced great advances in the treatment of patients with diabetes mellitus. In addition, and perhaps even more important, it has stimulated an immense volume of work carried out in research laboratories throughout the world and relating to a better characterization of the physiological and biochemical defect in the cells of the diabetic organism as well as to the specific mechanism of action of insulin and of other hormones It will be the purpose of this chapter to attempt a summary and organization of the present state of our knowledge in this area and it is evident that in so doing it will be necessary sometimes to oversimplify, and constantly to omit reference to a multitude of important studies and contributions

B DIABETIC SYNDROME

Elsewhere in this volume much emphasis is given to the clinical features of diabetes mellitus in man. These features may be subdivided into two syndromes (*a*) the acute diabetic syndrome and (*b*) the chronic diabetic syndrome Most of the features of the acute diabetic syndrome are present also in the chronic diabetic syndrome, but the latter is further characterized by body-wide morphologic alterations frequently interpreted as accelerated vascular aging Whether the acute and the chronic diabetic syndromes are directly related causally it is as yet uncertain, although likely in the opinion of many, and it should be clearly understood that most of our phyiologic and biochemical knowledge of diabetes mellitus is limited to the acute [illegible]

and by the relatively rapid sequence of events (described in Fig 5) which can quite easily, as a working hypothesis, be related to hyperglycemia as [illegible]

accepted. Indeed, it is entirely possible that factors other than the func-

later, however, having reached weights of 200–300 grams, a number of the partially pancreatectomized animals *suddenly* (usually within a very few, sometimes one or two days) develop hyperglycemia, glycosuria, a diabetic syndrome. It is difficult to explain this sequence of events on another basis than on that of a sufficient but limited insulin reserve placing a greater functional burden upon the remaining insulin-secreting cells and thus

diabetes mellitus and is accompanied by a deposition of iron pigment in the pancreas with secondary fibrosis and loss of functioning tissue, including particularly islet tissue In these instances, all rare, a correlation exists between development of diabetes and destruction of the pancreatic islets In the great majority of cases of diabetes mellitus, however, the correlation between morphologic damage to the islets and the development and severity of the disease is frequently poor Also, although a virtual absence of insulin is found at postmortem examination in the pancreas of some diabetic patients, this is not uniformly true [11] These observations are considered in much greater detail in the section on pathology Thus it would appear that in many instances the relation of functional adequacy of the beta-cells of the islets of Langerhans to the presence of the diabetic syndrome is not as simple as in the better understood forms of experimental diabetes The situation in man is perhaps comparable to that prevailing in those forms of experimental diabetes which have been related to "exhaustion" of the functional reserve of the pancreatic islets The observation that all the

practical application) strongly argues for the at present most widely accepted hypothesis concerning the endocrine defect in human as well as experimental diabetes mellitus, *i e that the diabetic syndrome is the result of either absolute or relative insulin deficiency* This in no way precludes, however, the presence of additional features or anomalies in all or some forms or cases of diabetes

D SOME ASPECTS OF INTERMEDIARY METABOLISM

The overall purpose of intermediary metabolism is that of making available to the organism the energy stored in organic compounds The latter

[10] Foglia Rev Soc Argent Biol, *20*, 21, 1944
[11] Wrenshall, Bogoch and Ritchie Diabetes, *1*, 87, 1952

diabetes are almost exclusively responsible. A syndrome closely simulating human diabetes mellitus (the acute diabetic syndrome) can be produced in experimental animals by one of the following procedures.

(1) The surgical removal of all or at least a large portion (usually nine tenths or better) of the pancreas, as first demonstrated by von Mering and Minkowski.[2] This observation first directed the attention towards the pancreas as the probable anatomic site of the endocrine defect in diabetes. Since ligation of the pancreatic duct, leading to complete atrophy of the endocrine portion of the pancreas, did not result in hyperglycemia, attention was then focused upon the islets of Langerhans. (2) The chemical destruction of all or at least a large portion of the β-cells of the islets of Langerhans, a destruction which can be achieved with substances such as alloxan[3] or dehydroascorbic acid[4] which in appropriate doses produce a selective necrosis of these cells. This observation closely links the diabetic syndrome to the cells usually thought to be the site of insulin production and secretion. (3) The inactivation of circulating insulin, by administration to animals of one species of antibodies against its own insulin, antibodies obtained by immunizing animals of another species against insulin extracted from pancreatic tissue of the first species This type of diabetic syndrome was first described by Moloney[5] in mice injected with antibodies to pig insulin obtained in guinea pigs and is, of course, reversible with discontinuation of the administration of the species specific insulin antibodies.

These observations certainly yield as good a biological correlation as can be hoped for with regard to our ability to produce experimental diabetes, on the one hand, and interference with the endocrine function of the pancreas—more specifically its secretion of insulin—on the other hand. There

[illegible]

secreting cells A similar mechanism has been postulated for the next type of experimental diabetes (5) The prolonged administration of glucose in quantities sufficient to maintain greatly elevated blood glucose levels throughout the greater portion of the 24 hour period Elevated blood glucose levels are known to stimulate insulin secretion and, again, eventual "exhaustion" of the insulin-secreting cells has been suggested This type [illegible] produced in only one species, the cat.[9]

[illegible] n postulated

[illegible] universally

[illegible] Arch f exper Path u Pharm, *26*, 371, 1889

[illegible] 43

[illegible] Physiol, *165*, 61, 1951

[illegible] 13, 1938

[illegible] ocrinology, *42*, 244, 1948

accepted Indeed, it is entirely possible that factors other than the functional capacity of the insulin secreting cells are involved However, the [illegible]

later, however, having reached weights of 200-300 grams, a number of the partially pancreatectomized animals *suddenly* (usually within a very few, sometimes one or two days) develop hyperglycemia, glycosuria, a diabetic syndrome. It is difficult to explain this sequence of events on another basis than on that of a sufficient but limited insulin reserve placing a greater functional burden upon the remaining insulin-secreting cells and thus leading to their eventual "exhaustion"

Human diabetes mellitus has been produced by pancreatectomy incident to removal of malignant tumors and has been noted during and after severe pancreatitis In addition, hemochromatosis is a well established cause of diabe [illegible]
panc [illegible]
parti [illegible]
tween development of diabetes and destruction of the pancreatic islets In the great majority of cases of diabetes mellitus, however, the correlation between morphologic damage to the islets and the development and severity of the disease is frequently poor Also, although a virtual absence of insulin is found at postmortem examination in the pancreas of some diabetic patients, this is not uniformly true [11] These observations are considered in much greater detail in the section on pathology Thus it would appear that in many instances the relation of functional adequacy of the beta-cells of the islets of Langerhans to the presence of the diabetic syndrome is not as simple as in the better understood forms of experimental diabetes The situation in man is perhaps comparable to that prevailing in those forms of experimental diabetes which have been related to "exhaustion" of the functional reserve of the pancreatic islets The observation that all the signs and symptoms of the acute diabetic syndrome may be normalized by the administration of insulin (although in certain cases this may only be possible by following a program of insulin administration not suitable for practical application) strongly argues for the at present most widely accepted hypothesis concerning the endocrine defect in human as well as experimental diabetes mellitus, *i e that the diabetic syndrome is the result of either absolute or relative insulin deficiency* This in no way precludes, however, the presence of additional features or anomalies in all or some forms or cases of diabetes

D SOME ASPECTS OF INTERMEDIARY METABOLISM

The overall purpose of intermediary metabolism is that of making available to the organism the energy stored in organic compounds The latter

[10] Foglia Rev Soc Argent Biol , 20, 21, 1944
[11] Wrenshall Bogoch and Ritchie Diabetes, 1, 87, 1952

are derived originally from the energy of light in photosynthetic processes. Photosynthesis results in the incorporation of carbon dioxide and water into hydrocarbons; intermediary metabolism results in an ordered and gradual *reversal of the energetics of the photosynthetic processes within living cells* and in the return of the photosynthetic energy to the organism in usable form. In order to attempt a description of the anomalies of intermediary metabolism in diabetes mellitus we shall attempt first to construct a usable blueprint of normal intermediary metabolism and, later, superimpose on this blueprint recognized metabolic errors in diabetes in an attempt to relate them intelligently to each other. In mammalian tissues it is convenient to consider separately the following steps within the intermediary metabolism of metabolic fuels:

1. **The Uptake of Glucose Into Cells and Its Metabolic Activation to Glucose-6-phosphate.**—It is important to understand that the transformation of extracellular glucose into intracellular glucose-6-phosphate (an activated form of glucose which contains more energy and has thereby become reactive in the presence of suitable enzymes, whereas glucose itself is not) implies both transport into the cell and activation in the presence of adenosinetriphosphate (ATP) and an enzyme (hexokinase). It has been well demonstrated[12] that the solubility characteristics of the membranes of *certain cells are such that glucose could not permeate them at a significant* rate unless a specific transport mechanism were available to it. It will be seen further on that both the transport of glucose into the cell and the activation of intracellular glucose to glucose-6-phosphate have been related to insulin action

2 **The Storage of Glucose-6-phosphate as Glycogen and the Mobilization of Glycogen.** Glucose-6-phosphate, once formed, can be stored as glycogen, a glucose polymer The glucose units of glycogen are so linked as to preserve the energy of the ester bond of glucose-6-phosphate, and glucose stored as glycogen may be transformed to glucose-1-phosphate and glucose-6-phosphate with little expenditure of energy The equilibrium between glucose-1-phosphate and glycogen is catalyzed by the enzyme phosphorylase as well as the branching and de-branching enzymes which control the macromolecular structure of glycogen Another pathway for the synthesis of glycogen from activated glucose in the form of uridinediphosphoglucose has recently been described[13] and may prove significant in our understanding of the regulation of glycogen synthesis and breakdown An effect of epinephrine, glucagon and also under certain conditions of insulin has been demonstrated at this level

3 **Metabolism of Glucose-6-phosphate to Pyruvic or Lactic Acid.**—This series of reactions is also known as "glycolysis" or "the Embden-Meyerhof pathway" Glucose-6-phosphate is further activated to fructose-1-6-diphosphate, then split in the presence of the enzyme aldolase into two phosphorylated 3-carbon fragments, oxidized and transformed into pyruvic acid The overall pathway involving at least 12 enzymes is reversible, although separate reactions for metabolism in either direction are provided

[12] Ross Jour Physiol, *112*, 229, 1951
[13] Leloir and Cardini Jour Am Chem Soc, *79*, 6340, 1957

at three points: the reactions between phosphopyruvate and pyruvate, the reactions between fructose-6-phosphate and fructose-1-6-diphosphate, and the reactions between glucose and glucose-6-phosphate In the latter two instances glucose is transformed to the more active form in the presence of a kinase and to the less active form in the presence of a phosphatase. The presence of these three points at which metabolism proceeds by different pathways in alternate directions are pointed out because of their possible usefulness as flow valves in the directional control of glycolysis

4. **The Synthesis of Glycogen and Glucose from Pyruvic or Lactic Acid.**— For the reasons just mentioned it is better to consider inverse glycolysis

glucose from precursors other than glucose to these tissues Lactating mam-

phosphate the Phosphogluconate-oxidative Pathway.—It has recently become more and more apparent that glucose-6-phosphate also undergoes oxidation to gluconic acid-6-phosphate and subsequent oxidative decarboxylation to a phosphorylated pentose in many tissues[15,16] The further metabolic transformations of this phosphorylated pentose eventually result in its re-entrance into the previously discussed pathways of glycolysis, thus permitting continuing regeneration of glucose-6-phosphate and complete oxidation of glucose to carbon dioxide and water by repeated rearrangements and recycling The biologic importance of this pathway results in part from the formation of important intermediary products and in part from the production during the oxidation of glucose-6-phosphate of reduced TPN (Triphosphopyridine nucleotide) a hydrogen carrier which is constantly gaining importance in the regulation of reductive biosynthetic reactions and more particularly in the biosynthesis of fatty acids It will be shown below that decreased activity of this pathway and the resulting decreased availability of reduced TPN has been related to the defect in the synthesis of fatty acids in diabetic tissues[17,18]

6 **The Metabolism of Pyruvate to Acetyl-coenzyme A and to Oxaloacetate** —Oxidative decarboxylation is the major fate of pyruvic acid in

readily in the further enzymatic reactions required by intracellular metabolism whereas acetic acid itself is not reactive Pyruvic acid can also react with CO_2 to yield oxaloacetic acid, a reaction which probably provides

[14] Krebs Bull Johns Hopkins Hosp, *95*, 19, 1954
[15] Dickens Internat Cong (3rd) Biochem, (Brussels), New York, Academic Press, pp 170 179, 1956
[16] Marks Diabetes, 5, 276, 1956
[17] Shaw and Gurin Jour Biol Chem, *226*, 417, 1957
[18] Siperstein and Fagan Science, *126*, 1012, 1957, Diabetes, 7, 181, 1958
[19] Lynen Harvey Lectures, *48*, 210, 1952-1953

the major part of the oxaloacetic acid needed to "spark" the tricarboxylic acid cycle and to keep it from "running down"

7. Further Metabolism of Acetyl-coenzyme A.—(*a*) *Oxidation of Acetyl in the Tricarboxylic Acid Cycle (Krebs Cycle).* In the [illegible]

[illegible] regenerated at the end of each revolution, a considerable amount of oxaloacetate may also disappear in the process, thus [illegible] other sources mandatory [illegible]

[illegible] formation of succinyl-coenzyme A, another activated intermediate which will be referred to below. (*b*) In addition to condensing with oxaloacetic acid, acetyl coenzyme A undergoes a number of reactions of which the most important, with regard to energy metabolism, are *the synthesis of long-chain fatty acids* and *the synthesis of acetoacetate.* Both reactions are initiated by the condensation of 2 molecules of [illegible]

[illegible] stepwise formation of fatty [illegible]

Although it was initially th[illegible] catabolism of fatty acids occurred simply by reversion [illegible]

[illegible] catalyzed by a different enzyme or by being carried out in a different location within the cell. Again, as in the case of glycolysis, this would provide a directional flow valve.

8. The Metabolism of Acetoacetate.—Acetoacetyl-coenzyme A may be formed either during the degradation of long-chain fatty acids or by condensation of 2 acetyl-coenzyme A molecules. Acetoacetate is then liberated by hydrolysis of the coenzyme A derivative in the presence of a specific deacylase which is mainly present in liver, thus confirming previous findings that ketone bodies are primarily released by hepatic tissue.[1] Acetoacetate can then be reactivated and used by all tissues either by direct reaction with coenzyme A in the presence of ATP, or by a transfer of coenzyme A to acetoacetate from succinyl-coenzyme A formed in the oxidation of citric acid, the latter, more economic transfer reaction is catalyzed by a sp[illegible] liver but is present in muscle and oth[illegible] transport system, acetoacetate be [illegible] mainly utilized in the periphery. Acetoacetate is also easily reduced to betahydroxybutyric acid and, finally,

[1] Note. A recent report of Lynen *et al* (Biochem. Ztschr., 330, 269, 1958) has modified this area of ketogenesis, and should be consulted.

[19] Lynen. Loc. cit. p. 105.
[20] Langdon. Jour. Biol. Chem., 226, 615, 1957.

can be decarboxylated to acetone, although this reaction is probably of small biologic significance.

9. The Metabolism of Amino Acids and Proteins.—With relation to the overall plan of intermediary metabolism it is necessary to mention here only that amino acids, in addition to their structural significance as building units of proteins, [illegible] 'iary metabolism and energy prod[illegible] which diabetes mellitus is the m[illegible] e a major one [illegible]

When gluconeogenesis is greatly increased, as is characteristically the case in diabetes mellitus, these pathways play a quantitatively important role Amino acids are found in concentrations manyfold higher in cells than in plasma, suggesting the presence of an active transport mechanism at the cell surface, similar perhaps to the active transport mechanism postulated [illegible] gested recently that, as in the [illegible] potentially important site of [illegible]

10 The Transport of Electrons from Substrate to Oxygen and the Liberation of Useful Energy.—The overall purpose of intermediary metabolism is that of generating useful energy as a result of substrate oxidation At the substrate level this oxidation usually results from the transfer of hydrogen to DPN or TPN resulting in the formation of reduced DPN or TPN Whereas reduced TPN is then mainly used for synthetic purposes such as [illegible]

of DPN, energy is liberated and fixed as chemically useful energy in the form of high energy bonds such as the high energy phosphate bond It is important to realize that high energy bonds other than phosphate bonds are also generated and used, an important one being the carbon-sulfur bond [illegible]

made further on to use this schematic representation for the organization of our knowledge relating to the anomalies present in diabetic tissues

E INTERRELATIONS IN INTERMEDIARY METABOLISM AND THEIR CONTROL

A glance at Figure 6 will be sufficient to convince one of the futility of

[21] Meister Biochemistry of the Amino Acids, New York, Academic Press, 1957
[22] Noall Riggs, Walker and Christensen Science *126* 1002, 1957
[22a] Kipnis and Noall Biochim and Biophys Acta, *28*, 226, 1958
[23] Lynen Loc cit p 105

any attempt to consider the metabolism of carbohydrates, fats and proteins as separate entities. It is evident that intermediary metabolism is best considered as a common metabolic pool, or better as a metabolic machinery

manufacture glucose from protein, a property essential to insure at all times adequate glucose supply for tissues such as brain tissues which obligatorily depend upon glucose for proper functioning. Finally, it should be stressed that this common metabolic machinery, providing for the inter-

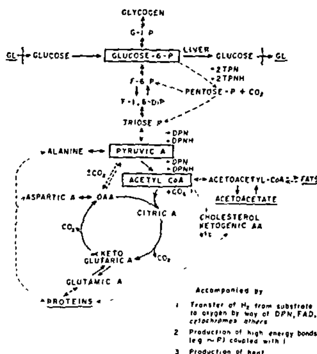


FIG 6 —Schematic representation of some reactions of intermediary metabolism. Features of several tissues have been combined. Dotted lines and arrows indicate particularly incomplete areas of the scheme and represent a number of reactions in each instance.

conversion of metabolic fuels and for their combustion in a single "furnace," relates mainly to the metabolism of carbohydrates, fats and proteins, as *fuels*. Different pathways and interrelations are likely to control some or most of the metabolic pathways concerned with the permanent structural

suitable for regulating this complex machinery must exist. According to present concepts it is likely that a large percentage of such control mech-

tension of this self-regulation by the induction of changes in the concentration of the appropriate enzymes, a mechanism which is known as *enzymatic adaptation* and which has been excellently reviewed recently by Knox, Auerbach and Lin [24]

Additional control mechanisms include many and probably most hormonal regulations Hormonal mechanisms probably also mediate between the nervous system and tissue intermediary metabolism The specific mechanisms by which hormones act have been elucidated only in part and in a very few instances It may be of interest at this time to outline some possible and perhaps likely areas suitable for metabolic control, since these areas may soon prove fruitful objects for further research

the rate of entrance of substrates into cells or, within the cell, their *rate of activation* resulting in metabolic availability It will be seen further on that both of these mechanisms have been considered in the case of insulin. (*b*) Once in the cell and activated, metabolic control could be achieved by affecting *the concentration or the activity of any enzyme catalyzing a rate-limiting reaction* Such a mechanism has been postulated for the action of epinephrine or glucagon upon the enzyme phosphorylase, and thereby upon the rate of glycogen breakdown or synthesis. It is immediately apparent, however, that such a control mechanism, which increases the activity of the catalyst, will not (everything else being equal) determine the direction in which the overall reaction is to proceed Thus, in the case of epinephrine and glucagon, increased phosphorylase activity could lead to either increased synthesis or increased breakdown of glycogen (*c*) Whereas control mechanisms leading to acceleration of reaction rates by controlling the activity of the catalyst are probably adequate in most instances (since concurrent metabolic processes such as increased availability of, or need for, certain substrates are likely to provide conditions which will determine the overall direction of the reaction) inherent *directional controls* are very probably desirable in certain situations Such directional controls may be expected with the greatest degree of likelihood in those areas of intermediary metabolism where two separate mechanisms have been provided for the catalysis of a given equilibrium, one catalytic system mainly affecting the reaction in one direction another catalytic system affecting the reaction in the reverse direction [25, 26] We shall consider three processes which may be used to achieve this separate catalysis of the two possible directions of a metabolic equilibrium between two substances *First*, the two catalytic systems may be located in *different tissues*, as is the case for the metabolic equilibrium between acetoacetate and acetoacetyl-

[24] Knox, Auerbach and Lin Physiol Reviews, 36, 164, 1956.
[25] Krebs Loc cit p 105
[26] Krebs and Kornberg Ergebnisse d Physiol, 49, 212, 1957.

CoA.[27] The presence of the enzyme deacylase (which frees acetoacetate from acetoacetyl-CoA) is by and large limited to liver tissue, whereas the enzyme CoA-transferase (which permits the rapid and energetically favorable reactivation of acetoacetate) is limited to peripheral tissues such as muscle. *Second, two different enzymes* may be provided in the same cell, as in the case of the equilibrium between glucose and glucose-6-phosphate, glucose phosphorylation being catalyzed by hexokinase, dephosphorylization of glucose-6-phosphate being catalyzed by glucose-6-phosphatase *Third, the same enzyme* may catalyze the equilibrium in both directions, but its location within the cell *in different cellular compartments*, providing different environmental conditions, may result in effective separation of the two directions of an equilibrium. Thus, an enzyme catalyzing a dehydrogenation may preferentially effect the removal of hydrogens from the substrate if it is located within or close to mitochondria (which provide a highly oxidizing environment), yet preferentially effect the hydrogenation of the product within or close to microsomal structures (which provide a highly reducing environment).[28] It would seem likely, that whenever such *directional flow valves* are provided within the scheme of intermediary metabolism, regulatory hormonal effects should be suspected in that area.

For further reading on pathways of intermediary metabolism a short and incomplete list of recent reviewing references may be helpful.[29–38]

F. INTERMEDIARY METABOLISM IN DIABETES MELLITUS

A number of the metabolic alterations which have been described in diabetes mellitus have been tabulated in Table 27 and related to each other in Figure 7 It should be stated at the onset that the summary so provided is based on a multitude of experiments carried out in the intact animal organism, as well as in isolated tissue preparations (perfused organs, thin pieces of intact tissue, tissue slices, tissue cultures) and from cell-free tissue preparations (homogenates and subfractions of homogenates). Much of this material has been recently reviewed [39–41] The relevance of most of these measurements to diabetes mellitus in man has yet to be established Each result has to be considered within the narrow context of the conditions of each experiment and quite particularly within the context of the particular species used and of the particular tissue used It is of special importance

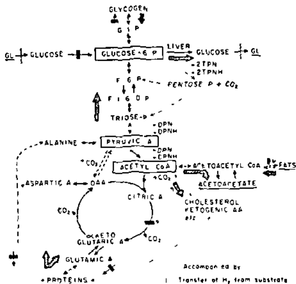
[27] Lynen Ibid , *327*, 1957
[28] [illegible] 388, 1955

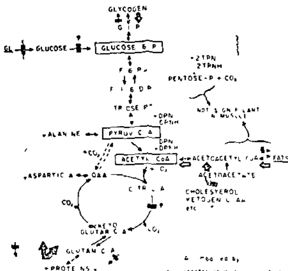
238, 177, 1958
955

954
6, Hormone Factors in Carbo-

Hormones, *14*, 139, 1956

, *230*, 751, 761, 1958


GLYCOGEN
G 1 P
GL
GLUCOSE
GLUCOSE-6 P
LIVER
GLUCOSE
GL
2TPN
2TPNH
F 6 P
PENTOSE P + CO_2
F 1 6 D P
TRIOSE-P
DPN
DPNH
ALANINE
PYRUVIC A
DPN
DPNH
CO_2
ACETYL CoA
ACETOACETYL CoA
FATS
CO_2
ACETOACETATE
ASPARTIC A
OAA
CITRIC A
CHOLESTEROL
KETOGENIC AA
etc
CO_2
∝KETO
GLUTARIC A
CO_2
GLUTAMIC A
PROTEINS
Accompanied by
1 Transfer of H_2 from substrate to oxygen by way of DPN FAD cytochromes others
2 Production of high energy bonds (e.g. ~P) coupled with 1
3 Production of heat


GLYCOGEN
G 1 P
GL
GLUCOSE
GLUCOSE 6 P
2TPN
2TPNH
PENTOSE-P + CO_2
F 6 P
F 1 6 D P
DPN
ALANINE
CO_2
ACETYL CoA
ACETOACETYL CoA
FATS
ACETOACETATE
ASPARTIC A
OAA
CHOLESTEROL
etc
CO_2
∝KETO
CO_2
PROTEINS

Fig

to consider in each instance the *tissue* in which a specific defect was described, since the intelligent consideration of the effects of any hormone will have to include a complete description not only of the chemical structure of the hormone itself, and of all its metabolic effects on tissues in general, but also of the specific metabolic effects which it exerts in each individual tissue. Only then will one be able to consider that most of the pieces of the puzzle have been collected and that the work of fitting them together can really begin.

TABLE 27.—SOME ALTERATIONS OF INTERMEDIARY METABOLISM IN DIABETES*

Symbols used. "−" decreased; "+" increased, "O" unchanged; "blank" not adequately measured; symbols in parentheses indicate that the finding has been seriously questioned

	Whole Organism	*Muscle or Adipose tissue*	*Liver*
Glucose transport	−	−	O
Glucose phosphorylation	−	−	−
Glycogen synthesis	−	−	−
Glycolysis to pyruvic acid	−	−	−
Synthesis of new glucose from pyruvate and other precursors	+	blank	+
Phosphogluconate-oxidative pathway	blank	−	−
Pyruvate to acetyl-CoA	(−)	blank	blank
Krebs cycle	blank	(−)	(−)
Acetyl-CoA to fatty acids	−	−	−
to cholesterol	(O)	blank	(+)
to acetoacetate	+	blank	+
Fatty acids to acetoacetate	+	blank	+
Oxidation of acetoacetate	O	O	O
Amino acids to protein	−	−	−
Protein to amino acids	+	+	+
Gluconeogenesis	+	blank	+
Oxidative phosphorylation	blank	(O)	(−)
Phosphorylation of thiamine	−	blank	−

*Most of the information upon which this table has been based has been recently reviewed.[33]

When one attempts to summarize the metabolic features described in Table 27 and Figure 7, first place may quite properly be given to the evident *disturbance in glucose utilization* by many tissues such as muscle, heart, adipose tissue, liver, a disturbance which is now quite generally accepted It is important to realize, however, that some tissues such as brain, renal tubular cells and intestinal mucosa, apparently absorb and activate glucose

levels which can be usefully achieved, and particularly in excess of the renal threshold Since either glucose uptake into cells, or its activation, or both

more detail

The synthesis of long-chain fatty acids by either liver or adipose tissue, from precursors such as pyruvate or acetate, is almost completely suppressed [42–44] An attractive explanation for this metabolic defect in terms of inadequate glucose utilization has been recently presented,[45–48] since it has been demon-

group,) has to be provided at least in part in the form of reduced TPN, whereas reduced DPN alone is insufficient as a hydrogen donor. The major source of reduced TPN available for fatty acid synthesis is the reduced TPN generated during the oxidation of glucose-6-phosphate by way of the pentose-phosphate oxidative pathway. It is evident that, when glucose utilization is defective, the oxidation of glucose-6-phosphate by way of the phosphogluconate oxidative pathway is also decreased, and the resulting lack of reduced TPN may be adequate to explain the apparent relationship (both in diabetes and in situations such as fasting) between the activity of glucose metabolism, on the one hand, and the activity of fatty acid synthesis, on the other A specific site for this metabolic defect in diabetes has been proposed by Shaw and Gurin,[49] namely the reduction of crotonyl-CoA to butyryl-CoA during fatty acid synthesis

Although there is general agreement with regard to the defective fatty

diabetic rats may synthesize more cholesterol than normal This finding has not been substantiated, however, in the intact organism[51] and, under different conditions, Siperstein[52] has found decreased cholesterol synthesis in the liver as well It would seem quite clear, however, *that cholesterol synthesis is inhibited to a lesser degree than fatty acid synthesis, and that under certain conditions it may be increased in the diabetic state* This observation may find its explanation in the apparent requirements for a specific mixture of hydrogen offered in the form of reduced DPN and hydrogen offered as reduced TPN for the biosynthesis of either lipid It may be assumed that

[illegible] Brady and Gurin Ibid *187*, 589 1950
[illegible] Chernick and Chaikoff Ibid , *188*, 389 1951
[illegible] Hausberger and Milstein Ibid , *214*, 483, 1955
[illegible] Shaw and Gurin Loc cit p 105
[illegible] Siperstein and Fagan Loc cit p 105
[illegible] Langdon Loc cit p 106

the conditions existing in the diabetic liver are less favorable to the synthesis of fatty acids than to the synthesis of cholesterol, and that under certain conditions at least the relative and perhaps even the absolute amount of cholesterol synthesized may be increased.

Whereas fatty acid synthesis is decreased in diabetes, *fatty acid mobilization and catabolism* is markedly increased.[53,54] Under these conditions the production of acetoacetyl-CoA from either long-chain fatty acids directly, or from acetyl-CoA, is increased, leading in the liver to an increased liberation of acetoacetate from this compound and thus to the characteristic increased ketogenesis of diabetes. Whether this increased production of acetoacetate is further accentuated by a defect in the oxidation of acetyl radicals in the Krebs' cycle[55] is not as yet clearly established but quite likely. It has been generally thought that *the further utilization of acetoacetate at the periphery is unimpaired*[56] although the maximal rate of this utilization would appear to be inadequate to handle the grossly excessive production of the compound and of its reduced analog (beta-hydroxybutyric acid) during acute diabetic decompensation.

It is well established that the diabetic state is further characterized by *decreased protein synthesis and by increased protein catabolism to amino acids*.[57,58] It is likely, although not established, that a considerable portion of the increased amino acids thus made available to intermediary metabolism is used for the synthesis of glucose, for gluconeogenesis. Without doubt, gluconeogenesis, *i.e.* the synthesis of new glucose from non-glucose

anomalies are undoubtedly present.[59,60]

Additional metabolic anomalies in diabetes have been described with regard to oxidative phosphorylation,[61] to the activity of the citric acid cycle,[62] to the availability of high energy phosphate reserves, to such processes as the phosphorylation of thiamine[63] or the acetylation of sulfanilamide.[64] For further details a number of recent reviews have become available among which the analyses and syntheses provided by Stadie

presented can be best integrated if one assumes that the primary defect in

423, 1940

54

199, 1956

Chem , 204, 533, 1953
54

40, 623, 1949

[66] Stadie Am Jour Med , 19, 257, 1955
[67] Stadie Diabetes, 5, 263, 1956

diabetes mellitus is one of inadequate glucose utilization by certain tissues This inadequate glucose utilization would secondarily lead to inadequate fatty acid synthesis because of the inadequate supply of hydrogen in the form of reduced TPN Inadequate glucose utilization would also lead to increased requirements for the utilization of other metabolic fuels and thereby to increased fatty acid release and catabolism as well as to increased protein catabolism to amino acids The stimuli responsible for the increased catabolism of protein and fats are as yet poorly understood

acid may be the basis of the probable, although not fully demonstrated decreased Kreb's cycle activity Decreased Kreb's cycle activity in turn would lead to decreased oxidative phosphorylation and to decreased reserves of high energy phosphate bonds The latter would explain such defects as the decreased phosphorylation of thiamine The overwhelming mobilization of fatty acids would lead to their massive catabolism in the *liver as well as other tissues, and a large portion of the acetoacetyl-CoA* formed would be released as acetoacetate When the general ability of the

that prolonged fasting, and particularly prolonged carbohydrate depletion without fat depletion may lead to significant ketosis and to metabolic evidence of decreased fatty acid synthesis[68] Competitive inhibition of glucose utilization by the administration of 2-deoxyglucose leads to hyperglycemia[69] Finally, and most significantly, the syndrome of *bovine ketosis* clearly demonstrates the relationship of severe carbohydrate depletion to ketoacidosis sufficiently severe to produce death This last metabolic situation is sufficiently instructive and sufficiently unknown among physicians, to warrant further elaboration[70,71]

Shortly after parturition and more specifically at the time when *abundant* lactation is initiated, the best milk producers of a herd of cows frequently

infusion of a large amount of glucose In order to understand the possible relevance of this syndrome to diabetic acidosis it is further necessary to know that although cows ingest a diet composed mainly of cellulose (and thus of carbohydrate), this cellulose is metabolized in the rumen, by the

[68] Lyon, Masri and Chaikoff Jour Biol Chem, *196*, 25, 1952
[69] Landau *et al* Jour. Nat Cancer Inst, *21*, 285, 1958
[70] Johnson Am Jour Vet Res, *14*, 366, 1953
[71] Pfander and Phillipson Jour Physiol, *122*, 102, 1953

rumen microorganisms, not to glucose but to a mixture consisting mainly of acetate, butyrate and propionate. The mixture of metabolic fuels absorbed from the gut therefore is metabolically mostly equivalent to dietary fat. During the initiation of milk production, these animals are called upon to produce as much as 30–40 liters of a 5 per cent carbohydrate solution (*i.e.* milk), as much as 1500–2000 grams of carbohydrate, a carbohydrate

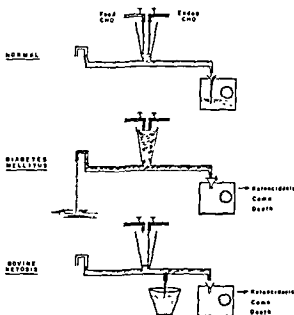


Fig. 8. Schematic representation of glucose supply to tissue cells in the normal organism, in the diabetic organism, and in bovine ketosis. Blood glucose is rep-

to the cells

s not slowed by the presence
ydrate balance may result
It is of more than casual

interest that the resulting syndrome so closely resembles acute diabetic acidosis!

The metabolic situations described have been schematized in Figure 8. Whereas, in the case of diabetic acidosis, the metabolic decompensation results from the inability of glucose to get into cells, the decompensation in

[illegible]

decompensation is readily reverted by either the intravenous infusion of [illegible]

G METABOLIC EFFECTS OF INSULIN

When considering the metabolic effects of insulin it should first be stressed that all metabolic abnormalities in diabetes mellitus, some of which have been described in the preceding section, can be completely corrected by the administration of insulin. One may therefore consider as established the statement that all *presently known* and reasonably well understood metabolic anomalies present in diabetes mellitus are either the direct or the indirect consequence of insulin deficiency, relative or absolute. It is, however, of obvious importance to organize the many known metabolic effects of [illegible]

[illegible]

of the hormone is increased. It should further be stated at the outset that *as yet no generally accepted effects of insulin upon cell-free systems have been described.*

Most striking effects of insulin upon isolated tissues have been described in muscle (both skeletal and cardiac), adipose tissue, mammary gland, white blood cells, and several connective tissue structures such as the lens, corneal epithelium, and the blood-aqueous barrier. This group of tissues, or preparations rich in these tissues (such as eviscerated preparations) would therefore appear particularly suitable for the study of direct insulin effects. In contrast, as has been previously mentioned, tissue preparations from brain, kidney, intestinal mucosa or red blood cells do not appear to be influenced in any way by the presence of insulin. Liver tissue is in an *intermediate category all its own, which will be further discussed below.*

Tissues which respond *directly to insulin added in vitro uniformly exhibit* increased glucose uptake from the medium and increased conversion of glucose to its various metabolic fates. Thus in adipose tissue[72, 73] the presence of insulin leads to increased glucose uptake as well as to increased glycogen deposition from glucose, increased oxidation of glucose to CO_2,

[72] Krahl. Ann. New York Acad. Sci., *54*, 649, 1951.
[73] Winegrad and Renold. Jour. Biol. Chem., *233*, 267, 273, 1958.

and increased fatty acid synthesis from glucose carbon. That these metabolic effects, as well as others not mentioned, may well be related to the increased glucose utilization is well illustrated by lipogenesis in adipose tissue. Insulin greatly stimulates lipogenesis from glucose in this tissue but fails to stimulate lipogenesis from acetate or pyruvate when these substrates are the only ones offered for metabolism. However, if glucose is

The timing of the effects of insulin upon glucose uptake and further metabolism by tissues such as muscle and adipose tissue coincides with the time course of the hypoglycemic effect of insulin *in vivo*.[75]

Insulin also increases the synthesis of protein from amino acids both by the rat diaphragm[76] and in the eviscerated dog.[77] Although this effect might also be related to increased glucose utilization, since increased glucose utilization *per se* leads to nitrogen retention and probably protein anabolism, the effect of insulin on protein metabolism may also be shown in the absence of glucose both *in vivo* and *in vitro*. A direct hormonal effect of insulin on protein metabolism is therefore likely.[78] In muscle and adipose tissue it would not appear that insulin affects the synthesis of glycogen by means other than the increased availability of glucose-6-phosphate after increased glucose utilization.

With regard to the effects of insulin upon hepatic tissue, the situation is

liver tissue have been demonstrated with regard to glycogen synthesis in rabbit liver,[83] the synthesis of peptides from amino acids in rat liver,[84] and the synthesis of long-chain fatty acids from acetate in rat liver. All of these effects are quantitatively small and, furthermore, are difficult to demonstrate in diabetic animals even though peripheral changes are easily demonstrated in diabetic as well as in normal animals. Since the liver cell

many investigators feel that insulin does exert a physiologically important

Chem., *213*, 135, 1955

logy, *9*, Internal Secretions

118

1950

Biophys Acta, *20*, 190, 1956

l., *192*, 191, 1958

direct action upon liver. Although the writer of this chapter is not among them, he certainly admits that the preservation of the secretion of insulin

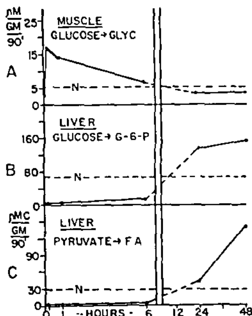


FIG 9 —Biochemical sequence of events after insulin administration to diabetic rats Three measurements selected are A, The incorporation of glucose into

135, 1955)

diabetic animals following the intravenous injection of insulin On the basis of this and similar experiments it has been suggested that the effect of insulin upon liver tissue is either mostly secondary to the effects of insulin upon peripheral tissues or that the nature of the insulin effect upon hepatic tissue significantly differs from its effect upon the periphery.[56]

[56] Renold, Hastings, Nesbett and Ashmore Loc cit p 118

Among further metabolic effects of insulin may be cited the production of respiratory quotients frequently greater than one, changes in the distribution of electrolytes such as potassium and phosphate, and, under certain conditions, an increased oxygen consumption.

II. MECHANISM OF INSULIN ACTION

A number of theories concerning the mechanism of insulin action have been evolved, one of which has relatively recently received such excellent experimental support and such wide acceptance as to justify its more complete presentation with only token consideration of the alternate solutions which have been suggested. It should be stated at the outset that this proposed mechanism of insulin action does not necessarily explain all of the known experimental facts, although it does contribute to the understanding of many.

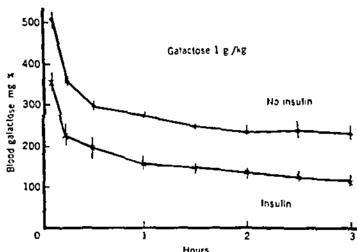
In 1949, Levine and Goldstein,[17] working with hepatectomized and nephrectomized dogs, studied the behavior of various solutes, more specifically sugars, with regard to their distribution in the extracellular and intracellular water of this preparation They noted that substances such as urea, which are not further metabolized by the mammalian organism, rapidly distributed into a given volume, reaching a given and constant plasma level The constancy of this plasma level was interpreted as indicative of the absence of further metabolism of the substance. When the solute used was glucose, a similar rapid initial distribution curve was noted, but was followed by a prolonged and rather constant further decrease in

only by the inversion of the H and OH groups on carbon 4 In the normal dog it was calculated from the blood levels of galactose obtained that the sugar distributed into approximately 30 to 35 per cent of body water, *i e.* into a compartment somewhat larger than the extracellular compartment. The administration of insulin resulted in a sharp further decline in the blood [illegible] ed (Fig. [illegible] ed that [illegible] size to [illegible] lism in the preparation used was adequately excluded the following conclusion with regard to the mechanism of insulin appeared warranted: insulin makes

[17] Levine, Goldstein, Klein and Huddlestun Jour Biol Chem, *179*, 985, 1949

established [88]

Since 1949, a number of observations relating to this phenomenon have been reported and have been recently reviewed rather completely by Ross,[89] and previously by Levine and Goldstein [90] Ross has further emphasized the anomalous behavior of glucose as a solute in mammalian physiology by demonstrating that the rate of its passage through cell membranes is usually



greatly in excess of what one would have expected on the basis of its solubility in cell membranes which generally exhibit the physical characteristics of lipids On the basis of the many observations summarized by these authors and relating particularly to the work of Levine and Goldstein in the hepatectomized dog, of Park and his collaborators working with the isolated rat diaphragm[91] and the perfused rat heart,[92] and Ross working with the rabbit lens the hypothesis that insulin exerts at least part of its action by facilitating the passage of glucose through certain cell membranes is now quite generally accepted Just how this is achieved is as yet a mys-

[88] Park and Johnson Am Jour Physiol, *182*, 12, 17, 1955
[89] Ross Medicine 35, 355, 1956
[90] Levine and Goldstein Recent Prog in Hormone Research, *11*, 343 1955
[91] Park and Johnson Loc cit p 121
[92] Morgan and Park Fed Proc, *17*, 279, 1958

tery, although Ross[92] has pointed out that the observed facts fit best the theory of activation of a catalytic but non-energy-requiring transport system for glucose The possible relationship of insulin and of diabetes to the permeability of cells to glucose (using permeability in a physiological, not in a restricted physico-chemical sense) had been suggested as early as 1914 by Hoeber.[94]

A certain number of observations, however, cannot be explained by the "permeability" theory of insulin action Among these one should cite the observations of Cori[95] with cell-free preparations of striated muscle, suggesting the presence of a direct insulin effect upon the hexokinase system, an effect depending at least in part upon the release of an inhibitory effect of pituitary origin Although these observations have proven remarkably difficult to reproduce in other laboratories[96] and although it seems appropriate to consider that an effect of insulin in cell-free preparations is not as yet established, these observations from Cori's laboratory focus our attention upon the step of glucose utilization which follows the entrance of glucose into cells, *i e.* the activation of glucose to glucose-6-phosphate Similarly, the presence of marked abnormalities of glucose utilization by liver cells, including a marked decrease in glucose phosphorylation,[97] cannot be reconciled with the "permeability" theory of insulin action without considerable strain: it is now clearly established that the liver cell membrane is freely permeable to glucose both in normal and in diabetic animals, and that equilibration of glucose across the liver cell membrane occurs within seconds or minutes [98] Free, non-phosphorylated glucose is always present within liver [illegible]
in the rate of the [illegible]
extracellular hepati[illegible]
hepatic utilization of glucose it is difficult to understand how the few and rather undramatic effects of insulin upon liver tissue *in vitro* could be related to an increased rate of glucose entrance into the liver cell or even to its activation However, since certain effects of insulin have been clearly [illegible]

Many of the consonant as well as dissonant facts and theories related to the mechanism of insulin action have been critically reviewed and analyzed by Stadie [100–102]

[93] Ross Loc cit p 121
[94] Levine and Goldstein Loc cit p 121, referring to Hober Biochem Ztschr, *60*, 231, 1914
[95] Price, Cori and Colowick Jour Biol Chem, *160*, 633, 1945
[96] Stadie and Hansgaard Jour Biol Chem, *177*, 311, 1949
[97] *Renold, Hastings and Nesbett Ibid*, *200*, 687, 1954
[98] Cahill, Ashmore, Earle and Zottu Loc cit p 118
[99] Baker, Chaikoff and Schusdeck Jour Biol Chem, *194*, 435, 1952
[100] Stadie Loc cit p 114
[101] Stadie Loc cit p 114
[102] Stadie Loc cit p 114

I REGULATION OF INSULIN SECRETION

Since it is assumed that inadequate insulin synthesis or release is a major pathogenetic factor in diabetes mellitus, it would be of obvious and indeed crucial interest to be fully informed with regard to the factors which affect the secretion of the hormone. However, knowledge in this area of the physiology of diabetes mellitus is scant indeed, a fact attributable in a major degree to our as yet extremely limited ability to measure the presence of the hormone in blood and tissues Satisfactory estimation of insulin levels has only been achieved in pancreatic tissue extracts, and the interpretation of these results is open to all the questions which generally affect the interpretation of hormone content of endocrine organs In particular, it is not possible to distinguish increased storage due to increased synthesis, from increased storage due to decreased secretion, nor is it possible to distinguish decreased storage due to increased secretion, from decreased storage due to decreased synthesis

Because of the chemically rather uncharacteristic structure of insulin a sufficiently specific chemical or physico-chemical assay for the small amounts of insulin present in blood has not as yet been devised and its development in the immediate future appears as yet unlikely Measurements of insulin in blood have therefore been limited to bioassay procedures *in vivo* and *in vitro*, procedures which all have in common lack of specificity,

[illegible]

neighborhood of 100–500 microunits per ml (between 1–5/10,000 of a unit per ml)

It appears established that *the blood level of glucose directly influences the secretion of insulin* from the pancreatic islets[108] Recently this has been particularly well illustrated by experiments in the laboratory of Lukens[109] demonstrating that the administration of small amounts of glucose into the pancreatic artery (amounts sufficient to raise the blood glucose level in the pancreatic vein but not in the general circulation) may result in marked and sustained hypoglycemia, presumably based upon increased insulin

[illegible]

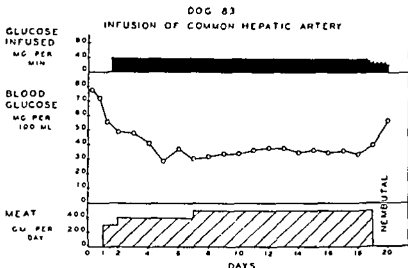
[illegible]

the Pancreas Boston Little Brown, 1956

[107] Martin Renold and Dagenais Lancet, 2, 76, 1958

[108] Reviewed by Foa Ciba Foundation Colloquia on Endocrinology 9 Internal

of a stimulatory effect of glucose upon some other structure (such as the pituitary or some area in the central nervous system) which would in turn stimulate the secretion of insulin. The existence of such extrapancreatic areas which affect the secretion of insulin has been often suspected, is indeed likely, but is not as yet established. Claude Bernard demonstrated as early as 1855, that lesions in the region of the hypothalamus may strikingly affect



man, DeMoor and Lukens, courtesy of Endocrinology, *50*, 649, 1952)

blood glucose levels, an observation which has been well confirmed and also further defined[112 113] Anterior pituitary (more particularly growth hormone) and adrenal cortical effects upon insulin secretion have also been quite frequently postulated but, as in the case of the influences of the nervous system, it has never been possible to satisfactorily rule out that the effects described were mediated by their direct metabolic effects, *e g.* by their effects upon blood glucose levels

action of orally release This

J ENDOCRINE FACTORS OTHER THAN INSULIN DEFICIENCY IN DIABETES MELLITUS

That endocrine glands other than the pancreas may be related to the production and/or to the symptomatology of diabetes mellitus was first

[112] Anderson *et al* Recent Progress in Hormone Research, *13*, 21, 1957
[113] Anderson, Rioch and Haymaker Acta Neuroveg, *5*, 132, 1952

strongly suggested when Houssay[114] demonstrated the striking amelioration of experimental diabetes mellitus which followed the removal of the anterior [illegible]

medullary hormones or sex hormones, while recent observations have stimulated considerable interest in the possible effects of the second pancreatic hormone, glucagon

It should be pointed out here that, as the study of internal secretions has [illegible] of in- [illegible] ellular [illegible] at the humoral regulatory mechanism is better considered as a whole in which each individual constituent is kept in continuous dynamic equilibrium with all other constituents It is therefore not surprising that numerous interrelationships between the pancreatic islets and the other endocrine organs have been described and that, according to the animals and condi- [illegible]

relationships which are at the present time established, even though it is understood that they represent but details of a picture considerably more complex when taken in its entirety

Anterior Pituitary.—As has already been pointed out, removal of the [illegible]

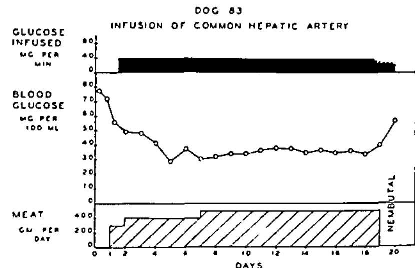
to insulin, and survive longer, even if not given any insulin at all They can become markedly sensitive to fasting and frequently die in hypoglycemia when fasted but for relatively short periods of time

In addition, Houssay[115] as well as several other groups of investigators[116-118] have shown that the injection of crude extracts of the anterior lobe of the pituitary gland may cause hyperglycemia and glycosuria in normal animals, and Young[119] demonstrated in 1937, that the daily injection of crude extracts of the anterior pituitary for 11 to 20 days may produce a [illegible]

changes in the pancreatic islets, and it has been suggested that the observed degranulation, hydropic degeneration, and death of the beta-cells might be due to initially excessive stimulation of insulin secretion Furthermore, it has been reported that the simultaneous administration of large doses of

[114] Houssay Endocrinologie 5 103 1929
[115] Houssay New England Jour Med, *214* 961, 1936
[116] Evans Meyer Simpson and Reichert Proc Soc Exper Biol and Med, *29*, 357, 1932
[117] Evans Ibid *30*, 1370 1933
[118] Barnes and Regan Endocrinology *17* 522, 1933
[119] Young Loc cit p 102

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[illegible]

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Recently great interest has been aroused by the possible action of orally effective hypoglycemic substances upon insulin synthesis or release This will be further discussed below

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[113] Anderson, Rioch and Haymaker Acta Neuroveg , *5*, 132, 1952

resulting need for evaluation of each growth hormone preparation in the species from which it was obtained[133,134]

Adrenal Cortex.—With regard to intermediary energy metabolism it is

intermediary metabolism and particularly upon carbohydrate metabolism, and their relation to the diabetic syndrome is best illustrated by the observation, first reported by Hartmann[135] and almost simultaneously conclusively demonstrated by Long and Lukens,[136] that bilateral total adrenalectomy decreases the severity of experimental pancreatic diabetes and increases the hypoglycemic response to a given dose of insulin. This is true in man as well The administration to normal subjects of large doses of adrenal cortical hormones with glucocorticoid activity results in hyperglycemia and glycosuria, but as yet a permanent diabetic syndrome, persisting after discontinuation of adrenal cortical hormone administration, has not been produced in previously normal experimental animals. Much information on this point is available in man on the basis of observations in Cushing's syndrome as well as in patients receiving large doses of adrenal cortical hormones during treatment of chronic inflammatory diseases In the few instances where discontinuation of hormone administration (or, in the case of Cushing's syndrome, adrenalectomy) was not followed by disappearance of the diabetic syndrome present during excessive adrenal

The metabolic effects of adrenal-cortical steroids on carbohydrate and intermediary metabolism have been recently reviewed[137–139] and details will not be presented here The best substantiated metabolic effect of these hormones is the production of increased hepatic gluconeogenesis resulting

recently suggested that the mechanism of action leading to increased hepatic gluconeogenesis may include increased "trapping" of amino acids by liver cells on the basis of increased efficiency of the amino acid transport system at the liver cell surface[140] A direct antagonism between glucocorti-

[133] Knobil Wolf and Greep Jour Clin Endocrin and Metab, *16*, 916, 1956 Endocrinology *62*, 348 1958

[134] Frosch *et al* Diabetes, *6*, 515 1957

d *37* 834 1934

1957

Endocrine Factors in

insulin along with anterior pituitary extract may protect the islet cells from irreversible degenerative changes.[120] It has also been found by Lukens, Dohan and collaborators[121] that the concurrent administration of phlorhizin, if begun before atrophy of the pancreatic islets develops, prevents the occurrence of morphologic changes of the pancreatic islets as well as the production of a diabetic syndrome in cats. Lukens suggested that blood glucose levels might play an important role, perhaps by way of possibly excessive stimulation of insulin secretion, in the development of the pituitary-induced diabetic syndrome. Direct effects of the anterior pituitary extract upon the islets of Langerhans, however, have also been suggested.[122, 123]

Although most of the fundamental early work was carried out with crude pituitary extracts, more recent work has led to the rather general acceptance of the thesis that at least a large portion of the "diabetogenic activity" of anterior pituitary extracts resides in its content in growth hormone[124, 125] (*i.e.* somatotropin). Direct metabolic effects of prolactin[126] on carbohydrate metabolism have also been described but are as yet less completely evaluated. *Indirect* effects of anterior pituitary hormone on intermediary metabolism also exist and are particularly prominent in the case of adrenocorticotropic hormone (ACTH) and thyroid stimulating hormone (TSH), and will be discussed along with the effects of their target glands. A further important metabolic activity of the anterior pituitary should be mentioned however, *i.e.* *adipokinetic activity*, since it may well play an important role in the occurrence of fat mobilization and ketogenesis in diabetes mellitus, and since increasing attention has been devoted to this activity of the anterior pituitary during recent years. As yet, adipokinetic activity has not been characterized as a separate hormonal entity, and it may well be an intrinsic part of several anterior pituitary hormones including growth hormone, ACTH and TSH.[127] It is of interest to note that ACTH has been conclusively shown to exert direct metabolic effects upon ketogenesis,[128] effects which can still be seen in totally adrenalectomized animals.

The information presently available with regard to the direct metabolic effects of growth hormone both *in vivo* and *in vitro*, in experimental diabetes as well as in human diabetes, is as yet frequently contradictory and confused and the reader is referred to recent extensive reviews of this topic.[129–132] Some of this confusion may well be due to the increasing likelihood of structural differences between growth hormones from different species and the

[illegible] nd Jour. Med., *223*, 607, 1940
[illegible] ology, *32*, 475, 1953

[illegible] sed. Physiol., *49*, 127, 1957
[illegible] tional Symposium, New York, McGraw-Hill, 1955

[126] Reviewed by Foa. Loc. cit. p. 123.

[127] Engel, Engel and McPherson: Jour. Clin. Endocrinology and Metab., *61*, 713, 1957.

Glucagon.—In recent years much interest has been devoted to the possible relationship of the second pancreatic hormone, glucagon, to experimental and clinical diabetes mellitus. This field has been recently and repeatedly reviewed[146-149] and it will suffice here to point out that the hormonal nature of glucagon is now rather widely (but not universally) accepted, although a deficiency syndrome resulting from glucagon lack has not as yet been securely established. The best characterized metabolic effect of glucagon is that of increasing hepatic glycogenolysis as a result of increased activity of the enzyme which catalyzes the transformation of inactive hepatic phosphorylase into its active form. Other metabolic effects, however, have also been described and may yet be shown to be of greater physiological importance. Studies performed in Dr. Best's labora-

[illegible]

relationship of glucagon to diabetes is as yet too uncertain to warrant further discussion here.

Gonads.—Many reports in the world literature suggest some relationship between the production of sex hormones and certain phases of the production, the severity, or the incidence of diabetes mellitus. Again the data appears too conflicting to warrant any serious interpretation or discussion in a textbook, and the reader is referred to several recent discussions of this topic.[150-152]

K. SOME FURTHER M[illegible] OBS[illegible] OF POSSIBLE IMPORTANC[illegible] IN UND[illegible] [illegible]NDING AND TREATMENT OF [illegible]

[illegible]

not be ascribed to any. Since that time, however, observations made in France and in Germany have led to the development of several drugs exhibiting distinct hypoglycemic activity, these drugs, which are also

[illegible]

this volume, but a brief statement as to the possible physiologic mechanism of action of these compounds will be given here.

[illegible] nb, 13, 473, 1957

[illegible] Endocrinology, 9, [illegible]56

[illegible] Ibid [illegible] 1951

coids and insulin, resulting in decreased glucose utilization, has yet to be conclusively demonstrated, although its existence has been suggested. Evidence is presently accumulating to indicate that increased insulin secretion may secondarily result from glucocorticoid administration, and that some of the effects hitherto ascribed to adrenal cortical hormones may really be related to compensatory hyperinsulinism.[141,142]

Much interest has been attached to the report by Becker[143] that a retinopathy similar in many respects to human diabetic retinopathy can be produced experimentally in alloxan-diabetic rabbits by the administration of cortisone. A possible relationship of adrenal cortical hyperfunction or dysfunction to the occurrence of the catastrophic late vascular complications in human diabetes mellitus has been suspected on the basis of these observations, and a small number of total bilateral adrenalectomies has been carried out in patients with rapidly [illegible] there is little evidence to indicate that [illegible] one, and it should be pointed out that [illegible] Addison's disease and diabetes mellitus has never been thought to be a particularly happy combination; vascular anomalies similar to diabetic vascular disease are not characteristic of Cushing's syndrome.

Adrenal Medulla.—Although the description of adrenal medullary effects upon carbohydrate metabolism historically antedates the description of adrenal cortical hormone effects upon carbohydrate metabolism, a fundamental relationship of adrenal medullary secretions to diabetes mellitus has never been established. Diabetic symptoms cannot be produced by the continued administration of epinephrine and removal of both adrenal medullae does not ameliorate the diabetic state of depancreatized animals.

The metabolic effects of the adrenal medulla are limited to the hormone epinephrine whereas nor-epinephrine has but little direct metabolic activity. Epinephrine accelerates the breakdown of muscle and liver glycogen, leading to increased blood levels of glucose and lactic acid. In addition epinephrine decreases the peripheral utilization of glucose and increases the release of fatty acids from adipose tissue. These effects may be important in connection with such situations as the ability to correct insulin-induced hypoglycemia or in the precipitation of diabetic acidosis by severe psychological disturbances.

One thing is established, namely that the arylsulfonylureas do not exert an insulin-like action by themselves It should perhaps be stated that the differences which exist between the hypoglycemic effects of insulin and the hypoglycemic effects of these newer, orally active compounds should not, as is sometimes the case, be viewed with dismay, but perhaps rather with hope, since beneficial hypoglycemic effects distinct from the well-known

page 310 Metabolic studies available to date suggest both hepatic and extrahepatic sites of action [171–172]

2 **Unesterified Fatty Acids in Blood or Plasma** —The important physi-

sis, and carbohydrate

Recently, however, a

herto given but little

attention, has been given emphasis and promises to add a metabolically highly significant parameter to our studies of lipid-carbohydrate interrelations Dole,[173] at the Rockerfeller Institute, and Gordon[174,175] at the National Institutes of Health, have introduced practical procedures for the measurement of that fraction of fatty acids in blood and plasma which is not esterified with glycerol but which is carried in the blood stream as unesterified fatty acid-albumin complex Although this lipid fraction

therefore in the conversion of triglycerides into a directly metabolizable fuel, and that it may account for a large percentage of the caloric requirements of the mammalian organism, indeed, under certain conditions, for the total caloric requirements of tissues such as heart Unesterified fatty acid levels are elevated in diabetes and promptly respond to the administration of glucose and insulin in a fashion which seems to parallel the promptness of glucose utilization These rapid changes, within minutes, reflect the high turnover rate of the fraction and suggest the usefulness of the index for acute estimation of metabolic events

[166] Deut Med Wchnschr, 82, 1514 1592, 1957
[167] Metabolism, 5, 721 977, 1956
[168] Canad Med Assn Jour, 74 957, 1956
[169] Diabetes, 6 1 94 1957
[170] Ann New York Acad Sci, 71 1 291, 1957
[171] Krall and Camerini-Dávalos Proc Soc Exper Biol and Med, 95, 345, 1957
[172] Williams, Tanner and Odell Diabetes, 7, 87, 1958
[173] Bierman, Dole and Roberts Ibid 6, 475, 1957 Jour Clin Invest, 35, 150 1956
[174] Gordon and Cherkes Jour Clin Invest, 35, 206, 1956
[175] Gordon Ibid, 36, 810, 1957
[176] Havel and Fredrickson Ibid, 35 1025, 1956
[177] Bierman, Schwartz and Dole Am Jour Physiol, In press
[178] Fredrickson and Gordon Physiol Rev, 38, 515, 1958.

There is considerable evidence to indicate that the mode of action of several of the oral hypoglycemic agents (carbutamide, tolbutamide and IPTD) is similar and the observations referred to here will be mostly concerned with tolbutamide, the compound which has now become generally available in the United States. It should be stated at the outset that the arylsulfonylureas probably exert several, perhaps many, effects and that no general agreement exists at the present with regard to the mechanism of the hypoglycemia produced. A detailed discussion of the many hundred publications which have rapidly appeared during the past few years does not appear warranted, since a useful conclusion (*i.e.*, a conclusion useful in guiding one's therapeutic thinking) cannot be reached at the present time. Two major theories have been proposed: (*a*) *The compounds exert a stimulating effect upon pancreatic insulin secretion.* This theory is based upon the observation that it is difficult, perhaps impossible, to demonstrate striking hypoglycemic effects of the compounds in the absence of the pancreas or in those patients with severe, ketotic diabetes mellitus of the juvenile type, whose insulin reserve is presumed to be almost completely depleted. Furthermore, it has been demonstrated that pancreatic insulin content decreases after arylsulfonylurea administration,[153] that degranulation of the beta cells of the islets of Langerhans occurs[154] and that increased levels of a substance with hypoglycemic activity may be demonstrated in the pancreatic vein.[155–157] (*b*) The second theory proposes that *these compounds mainly exert an extrapancreatic action upon tissues and particularly upon liver*, resulting in decreased hepatic glucose synthesis or release, as well as in many other metabolic effects on tissues and enzyme systems. This second theory is based mostly upon the failure of the insulin stimulation theory to account for such findings as direct effects of the arylsulfonylureas upon liver and other tissues,[158–161] effects quite distinct from the effects of insulin, upon the clear-cut demonstration of the inhibiting activity of these substances upon a number of isolated enzyme systems,[162, 163] effects again not shared by insulin, and upon the failure to demonstrate increased insulin levels in human plasma even when the sulfonylurea-induced hypoglycemia *is sufficiently severe to lead one to expect the presence of elevated circulating* concentrations of insulin-like activity.[164, 165]

[153] Pfeiffer *et al.* Deutsch Med. Wchnschr., *82*, 1568, 1957.
[154] Ashworth and Haist. Canad. Med. Assn. Jour., *74*, 975, 1956.
[155] Loubatières. Ann. New York Acad. Sci., *71*, 192, 1957.
[156] Pozza, Galansino and Foa. Proc. Soc. Exper. Biol. and Med., *93*, 539, 1956.
[157] Pfeiffer *et al.* Proc. Third Cong. Internat. Diabetes Fed., Dusseldorf, West G[illegible]

means of producing experimental diabetes in the laboratory. Because of the structural relationship of alloxan to uric acid, the possibility that alloxan might arise in the course of normal or abnormal intermediary metabolism has interested a r [illegible] uric acid metabolism [illegible] Although it has be [illegible] may produce a diabetic syndrome in rabbits,[181] this has not been confirmed[182] It was early noticed that the administration of alloxan produces a profound decrease in the blood levels of free sulfhydryl (SH) groups[183] and that the [illegible]

effect, is as yet unknown In view of the presence of free sulfhydryl groups in many proteins, and particularly in many enzymes, it has been thought that the diabetogenic effect of the compound may well be related to an effect upon these groups In 1949, Patterson[184] found that the intravenous injection of *dehydroascorbic acid* into rats causes permanent diabetes, a finding which has been well substantiated since. The physical and chemical properties of dehydroascorbic acid are closely similar to those of alloxan and a similar mechanism of action may be expected As in the case of alloxan it is as yet completely unknown whether under any normal or abnormal conditions significant amounts of dehydroascorbic acid may arise in the course of human metabolism

alloxan In this instance the discovery of the diabetogenic activity of the compounds was an incidental observation dithizone reacts with zinc to produce colored complexes, a property which has led to its use in the histological staining of zinc in tissues During studies related to the distribution of zinc *in vivo*, it was noted that the development of a diabetic syndrome followed the administration of the compound to experimental animals It is of interest to note that dithizone is selectively accumulated in the pancreatic islets, which are particularly rich in zinc, whereas alloxan has not been shown to be selectively accumulated in the pancreatic islet cells[186] In the case of dithizone, the diabetogenic activity has been related to its ability to complex with zinc but a more detailed analysis is as yet not available The pharmacology of alloxan has been repeatedly reviewed,[187, 188] as has also more recently, the relationship between insulin and pancreatic zinc content[188a]

[181] Griffiths Jour Biol Chem *172*, 823, 1948 *184*, 289, 1950
[182] Collins-Williams and Bailey Proc Soc Exper Biol and Med, *71*, 583, 1949
[183] Leech and Bailey Jour Biol Chem, *157*, 525, 1945
[184] Patterson Loc cit p 102
[185] Kadota Jour Lab and Clin Med 35 568, 1950
[186] Landau and Renold Diabetes 3 47, 1954
[187] Bailey Vitamins and Hormones 7, 365, 1949
[188] Ogilvie Ibid, *10* 183 1952
[188a] Maske Diabetes, *6*, 335, 1957

3 **Diabetogenic Agents.**—By definition a diabetogenic agent is an agent which produces prolonged hyperglycemia. This definition includes agents *which produce temporary hyperglycemia limited to their period of administration*, and agents which produce permanent diabetes mellitus, persisting after discontinuation of drug administration. Within the first group one finds a number of hormones as well as a number of m ... I poisons, among which fluoroac... *good example, as extensively* ... type of diabetogenic effect may be ... relationship to the metabolic disturbance in diabetes mellitus, intensive metabolic evaluation of the relationships involved in each single case is clearly indicated, since valuable information relating to pathways of intermediary metabolism and to their *interrelations is bound to result, and may suggest important correlations* and experimental hypotheses in the study of diabetes mellitus *per se*. The

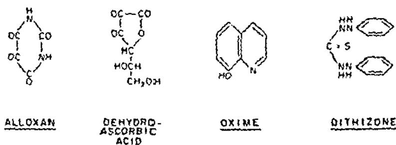


FIG 12 Substances which have been shown to produce necrosis of the beta cells of the pancreatic islets with resulting diabetic symptomatology

second type of diabetogenic substances, namely that which produces permanent diabetes, has (as yet) always been associated with structural changes *or anatomical destruction of the beta cells of the islets of Langerhans.* In addition to their interest as agents which permit the production of experimental diabetes in the laboratory, the observation of their effects may lead to improved understanding of the metabolic activity of the beta cells of the islets *of Langerhans themselves, and particularly of that part of their metabolic* activity which is related to the synthesis and secretion of insulin. It is of course entirely conceivable that the production in normal or ab*normal metabolism of substances exerting damaging effects upon the pancreatic islet cells might be involved in the etiology of at least certain forms* of diabetes. Four substances will be discussed (Fig 12).

Alloxan, the ureide of mesoxalic acid ...
glycemia, then hyper...
of Langerhans b ... since that
time ... compound have been
repor... most frequently used

144 E... and Cole Ibid., 170, 325, 1954
145 Engel, Fredericks and Cole Endocrinology, 60, 446, 1957
146 Dunn, Sheehan and McLetchie Loc cit p 102

means of producing experimental diabetes in the laboratory. Because of the structural relationship of alloxan to uric acid, the possibility that alloxan [illegible] olism [illegible] uric [illegible] Al- [illegible] may produce a diabetic syndrome in rabbits,[181] this has not been confirmed.[182] It was early noticed that the administration of alloxan produces a profound decrease in the blood levels of free sulfhydryl (SH) groups[183] and that the concurrent administration of substances rich in free sulfhydryl groups (or [illegible] Alloxan [illegible] sulfhydryl [illegible] re specific effect, is as yet unknown. In view of the presence of free sulfhydryl groups in many proteins, and particularly in many enzymes, it has been thought [illegible] id may well be related to an [illegible][184] found that the intravenous [illegible] causes permanent diabetes, a finding which has been well substantiated since. The physical and chemical properties of dehydroascorbic acid are closely similar to those of alloxan and a similar mechanism of action may be expected. As in the case of alloxan it is as yet completely unknown whether under any normal or abnormal conditions significant amounts of dehydroascorbic acid may arise in the course of human metabolism.

[illegible]

alloxan. In this instance the discovery of the diabetogenic activity of the compounds was an incidental observation. dithizone reacts with zinc to produce colored complexes, a property which has led to its use in the histological staining of zinc in tissues. During studies related to the distribution of zinc *in vivo*, it was noted that the development of a diabetic syndrome followed the administration of the compound to experimental animals. It is of interest to note that dithizone is selectively accumulated in the pancreatic islets, which are particularly rich in zinc, whereas alloxan has not been shown to be selectively accumulated in the pancreatic islet cells.[186] In the case of dithizone, the diabetogenic activity has been related to its ability to [illegible] not available [illegible] [187, 188] as has also [illegible] creatic zinc content.[188a]

[181] Griffiths, Jour. Biol. Chem., *172*, 823, 1948; *184*, 289, 1950.
[182] Collins-Williams and Bailey, Proc. Soc. Exper. Biol. and Med., *71*, 583, 1949.
[183] Leech and Bailey, Jour. Biol. Chem., *157*, 525, 1945.
[184] Patterson, Loc. cit., p. 102.
[185] Kadota, Jour. Lab. and Clin. Med., *35*, 568, 1950.

949

4 **Metabolism of Fructose and Sorbitol.**—The recent advances which have been made in the understanding of the metabolic processes concerned with the utilization of the three hexoses mainly involved in mammalian energy metabolism, glucose, fructose and galactose, have led to renewed interest in the possible clinical usefulness of fructose in the treatment of diabetes mellitus It has been postulated, since Minkowsky's demonstration of glycogen formation from fructose in pancreatectomized dogs, that diabetic tissues utilize fructose at nearly a normal rate. In a number of

metabolize glucose, as quite particularly evidenced by changes in nitrogen excretion and in respiratory quotient values. Although a number of studies have been performed with the purpose of demonstrating the additional usefulness of fructose as adjuvans in the therapy of diabetes mellitus, the abundant literature which has accumulated over the past 50 years has failed to yield a conclusive answer A fresh appraisal is presently being carried out in a number of clinics and laboratories and has been based on more recently acquired metabolic knowledge of the pathways involved [190–194]

First of all, it has been clearly established that fructose is used almost exclusively by the liver, and that this is due to the presence in liver (and also, although to a lesser degree, in kidney and intestinal mucosa) of a specific enzyme, fructokinase, which phosphorylates fructose to fructose-1-phosphate and which is not insulin dependent. The fructose utilization by tissues other than liver is relatively small, a fact which may be explained by the lack of a specific fructokinase in these tissues and by the competition between glucose and fructose for phosphorylation by hexokinase to either glucose-6-phosphate or fructose-6-phosphate; the affinity of glucose for the enzyme is greater than the affinity of fructose, leading to poor fructose utilization as long as glucose is present. In the liver, after phosphorylation to fructose-1-phosphate, the major portion of further fructose metabolism involves the splitting into two 3-carbon fragments which then enter the normal glycolytic pathways These 3-carbon fragments may then proceed either to pyruvate and acetyl-CoA or to glucose-6-phosphate, glycogen and glucose

Essentially normal hepatic utilization of fructose in the absence of insulin is unquestioned [195] Questions as to the real benefit of fructose thus phosphorylated have arisen mainly from the possibility that much or most of the ... phate and

... 323, Diabetic

... 27, 1953

... berg, p 145, 1956

[193] *Cori, Ochoa, Slein and Cori* Biochem et Biophys Acta, 7, 304, 1951

[194] Pletscher Helv Chim Acta, *20*, 100, 1953

[195] Renold, Hastings and Nesbett *Loc cit* p *114*

on the quantitative relationship of (*a*) fructose retained in the liver or released as pyruvate and other intermediates which may be utilized by other tissues in the absence of insulin to (*b*) fructose released as glucose

In addition it is as yet unsettled what percentage of fructose is converted to glucose during intestinal absorption of fructose, since the intestinal tract accounts for the metabolization of a large proportion of fructose in certain animal species [196] Finally, fructose is a rather expensive carbohydrate

Recently it has been suggested that sorbitol (see Fig 13) the polyalcohol

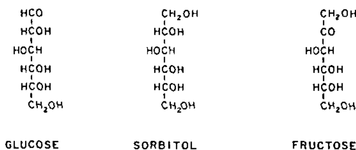


Fig 13

resulting from the hydrogenation of either glucose or fructose, may be used as a fructose substitute with perhaps some advantages over fructose [197–199] Sorbitol is metabolized by way of fructose and is metabolized almost exclus

not

the

adults, may represent a real advantage since it produces a continuous, slow mode of administration, which is likely to result in a much greater retention of sorbitol and fructose in the liver than is the case when acute loads are administered The cost of sorbitol is a fraction of that of fructose.

One might summarize the present status of the possible usefulness of sorbitol or fructose as an adjunct in the treatment of diabetes mellitus as being theoretically based upon the ability to improve carbohydrate utilization by hepatic tissue over and above the degree of control attained by insulin administration This particular attention to hepatic carbohydrate utilization has been shown

secondary abnormalities of

cessive ketogenesis, abnorm

[196] Kiyasu and Chaikoff Jour Biol Chem 224, 935, 1957
[197] Olmsted Diabetes 2 132 1953
[198] Adcock and Gray Biochem Jour 65 554 1957
[199] Renold *et al* Diabetes (In press)

and availability of high energy phosphate.[200–202] Since abnormalities of [illegible]

demonstration of such benefits, however, will have to await the accumulation of a large number of well controlled clinical observations. For the present, fructose, sorbitol and galactose may already fill a useful diagnostic function in the form of glucose, sorbitol and galactose tolerance tests, with measurement of both sugar utilized and glucose formed as an index of the activity of hepatic gluconeogenesis.[203, 204]

5. **Further important metabolic observations.**—These are not considered in detail because of lack of space, but to which attention should be drawn and reference given, will be mentioned in this section. Increasing interest is being directed toward the metabolic behavior, as well as the possible metabolic effects, of *amino sugars*,[205–207] which occur in blood in concentrations equal to glucose, although they are almost exclusively present in the form of complexes with proteins. The study of amino sugar metabolism and behavior is likely to yield important information both with regard to their possible metabolic effects, as related to the diabetic syndrome, and also with regard to their possible relationships to late vascular complications in diabetes as has already been discussed in the chapter on pathology. Reference should be made to the extensive work on enzymes with insulin-destroying activity (*insulinase*), studies which have been quite particularly championed by Mirsky.[208–210] Although the physiologic importance of insulinase is as y[illegible]
capable of hydro[illegible]
present in many [illegible]
survival of the insulin molecule in blood and tissues, and thereby the duration of insulin action. In this same general area of interest, the metabolic fate of *insulin labelled with* I^{131} has been extensively studied,[211–214] particularly by Williams and his collaborators in Seattle, and it has been established that the half life of insulin I^{131} in plasma is prolonged in patients who have undergone insulin therapy for a considerable period of time. This suggests that proteins reacting more or less specifically with insulin and leading to

[200] Baker, Chaikoff and Schusdek. Loc. cit. p. 122.
[201] Helmreich, Goldschmidt, Lamprecht and Ritzel. Ztschr. Physiol. Chem., *292*, 184, 1953.
[illegible]

alterations in the rate of insulin transfer across blood vessel walls and cell membranes may play an important, as yet ill defined, role in the overall effectiveness and physiology of insulin secretion. Similarly *substances which are capable of inhibiting insulin activity* have repeatedly been demonstrated in the circulation and have been related either to previous insulin therapy [215,216] (suggesting the presence of "antibodies") or to the endocrine state, more particularly to pituitary activity,[217,218] (suggesting the presence of

[illegible]

other proteins in blood and tissues are likely to yield particularly important information in the near future The subject of insulin inhibitors has just been critically reviewed by Berson and Yalow [223]

[illegible] 1952

Ibid, 35, 170, 1956

ernational Symposium, New

l, *166*, 191, 1951

Metabolism, 7, 266, 1958

Chapter 5

APPLIED PHYSIOLOGY IN DIABETES

ALEXANDER MARBLE, M.D.

A. INSULIN

Properties.—Thirty years prior to the discovery of insulin in 1921 by Banting and Best,[1] its production by the cells of the islands of Langerhans, first described in 1869,[2] had been suggested by Laguesse.[3] In the intervening period many workers tried with greater or less success to extract the active principle. We realize now that some almost succeeded but in the treatment of diabetic patients these researches found little or no practical application, largely for two reasons: (1) the administration of extracts by mouth—now recognized for practical purposes to be useless even with material of known potency—was often the method of trial, (2) extracts were so crude as to give rise upon injection to unpleasant symptoms of toxicity. Perhaps Zuelzer[4] came as close as any to the cherished goal. He even treated successfully several diabetic patients by injection of his extracts but he and other clinicians found the product too toxic for general use.

In the purification of their extract Banting and Best were aided by Collip,[5] Scott[6] and others. As time went on the market preparation became more and more highly purified. Scott and Parker[7] outlined a method employed at the Connaught Laboratories for securing highly purified insulin preparations. Insulin was first obtained in crystalline form by Abel and his co-workers[8] in 1926.

Scott[9] showed that insulin crystals contain traces of zinc and that unless small amounts of zinc, cadmium, cobalt or nickel are present, crystallization is not possible. He demonstrated that the crystals occur in twins with the flattened surfaces of the rhombohedral plates in apposition. The melting point is 233° C. and the iso-electric point is at pH 5.3-5.8. Insulin is optically active and laevorotatory. There has been much discussion as to the molecular weight of insulin. Detailed studies have led to the conclusion that the insulin molecule is formed from subunits of equivalent weight

12,000.[10] Since a molecular weight of 48,000 is obtained by ultracentrifuge studies and one of 36,000 by roentgen-ray analysis, it is assumed that particles of insulin in solution consist of four subunits while the crystal is

acid or by boiling. It dissolves readily in dilute acid, dilute alkali and 90 per cent phenol. It is somewhat soluble in 80 per cent alcohol and insoluble in water-free organic solvents. It seems unlikely that the active principle is merely adsorbed on the protein. Rather, it seems fairly certain that the protein is identical with the hormone, insulin.

Sanger[14] concluded that the insulin molecule is made up of two polypeptide chains, a glycyl chain (Fraction A)[15] and a phenylalanyl chain

t the sulphur, 3.2 per
Abel and co-workers
activity and the so-
called labile sulphur. Other groups which have been regarded as probably possessing especial activity are the amino and tyrosine groups.

Analyses of insulins obtained from cattle, pigs and sheep have shown qualitative differences in the content of certain amino acids.[19] However, insulin crystals obtained from these animals (and from fish) have the same biological activity and the same sulphur content. The evaluation of the potency of a given insulin preparation is made by comparing its hypoglycemic action with that of the International Standard crystalline preparation (adopted in 1935) to which has been assigned the potency of 22 units per mg. Fractionation and purification studies have yielded samples with potency as great as 27 units per mg.[20]

If the protein structure of insulin is affected by hydrolysis through chemical or enzymic means, the physiological activity is lost. In this fact undoubtedly lies the reason for the ineffectiveness of insulin given by mouth. (See page 138.)

[10] Haurowitz. Chemistry and Biology of Proteins, New York, Academic Press, Inc., p. 54, 268, 1950.
[11] Fredericq and Neurath. Jour. Amer. Chem. Soc., 72, 2684, 1950.
[12] Fredericq. Chapter in Ciba Foundation Colloquia on Endocrinology, 9, Boston, Little, Brown, pp. 89-109, 1956.
[13] Waugh. Ibid., pp. 122-132.
[14] Sanger. Biochem. Jour., 45, 563, 1949.
[15] Sanger and Thompson. Ibid., 53, 353, 1953.
[16] Sanger and Tuppy. Ibid., 49, 463, 1951.
[17] Sanger. Ciba Foundation Colloquia on Endocrinology, 9, Boston, Little, Brown, pp. 110-121, 1956.
[18] Lindner. in Insulin und Insulintherapie, München-Berlin, Urban and Schwarzenberg, pp. 17-34, 1956.
[19] Harfenist and Craig. Jour. Amer. Chem. Soc., 74, 4216, 1952.
[20] Fredericq. Loc. cit., p. 139.

Insulin is the product of the beta cells of the islands of Langerhans of the pancreas Final and conclusive proof of this is afforded in the rare condition of carcinoma of the island (beta) cells; not only does the untreated condition result in profound chronic hypoglycemia, but insulin may be extracted in significant quantities from the tumor masses (as metastases in the liver) when removed from the body.[21] The granules in the beta cells are alcohol-soluble

of the blood stream a

microscopic study of

in response to the subcutaneous injection of dextrose, large vacuoles formed in a given islet cell and migrated to the periphery of the cell next the blood capillary where they were diminished in volume, presumably by diffusion of their contents through the cell membrane Best[22] regards the production of insulin by any tissues other than the islands of Langerhans ("cellular insulin")[24] as not proved.

Monographs regarding insulin have been written by Staub,[25] Aubertin,[26] Jensen and Evans,[27] Hill and Howitt,[28] and Jensen [29] The reader is referred to these and to the article by Scott[30] for further details Papers and discussions at certain conferences[31] [32] are likewise of great interest.

Insulins With Prolonged Action.—Soon after the introduction of insulin in 1922 the relatively short duration of action of the preparation with the consequent necessity for repeated injections became apparent. Efforts were made to retard the action or to develop a preparation which would exert its effect over a longer period of time Among the authors' patients attempts were made to delay the absorption of insulin by injecting it into thick fatty tissue instead of the subcutaneous spaces, but these trials were unsuccessful. Insulin was mixed with 20 per cent solution of gum arabic in 1923,[33] and in 1925 delayed absorption was sought by the addition of protein,[34] and, indeed, the combination of both gum arabic and protein yielded somewhat encouraging results. Bernhard in 1926 tried a mixture of insulin and fat In 1929 Leyton[35] employed various oils to delay absorption with effect, and this was confirmed by others. A combination of lecithin and insulin was likewise used[36] but again without practical results Com-

Assn, 89, 348, 1927 Power,
Cragg 1936

Am Med Assn, 99, 935,
1932

and Technical Publications,
London, 1936

[29] Jensen Insulin Its Chemistry and Physiology, New York, The Commonwealth Fund, 1939

[30] *Scott Loc cit*, p 138

on, Little, Brown, 1956
ty München, München-

205, 777, 1923

Skouge and Schrumpf

binations of pituitrin and adrenalin were devised, but these, too, proved unsatisfactory.[37] Bischoff and Maxwell[38] reported prolongation of action of insulin in rabbits and rats by the addition of basic ferric chloride or tannic acid. The first real advance came in 1935 with the preparation and clinical trial of protamine insulin by Hagedorn and associates at the Steno Memorial Hospital, Gentofte, Denmark. The action of this preparation extended over some twelve to fifteen hours. With the addition of a small amount of zinc, the length of action was greatly prolonged. The present market protamine zinc insulin has a duration of effect of twenty-four to forty-eight hours. For details of this and other insulins with prolonged action, see page 282.

Insulin Content of the Pancreas.—Scott and Fisher[39] carried out analyses for insulin and zinc in the pancreases of 14 normal and 18 diabetic persons. They found t[illegible] per gram of [illegible] e being 0.14 mg. of [illegible] with 0.07 mg. per gram of diabetic pancreas. Haist[40] summarized the values obtained by [illegible] values are more nearly uniform.

Haist, Best and associates[41, 42] in a series of studies found that in rats, fasting, fat-feeding and the administration of insulin caused a reduction in the [illegible] for [illegible] the [illegible] administration of anterior pituitary extract. They concluded that in the studies both in the rat and the dog, the effects observed following the three procedures were due to resting the islets.

Latta and Harvey[43] noted that when albino rats were subjected to re[illegible] beta cells the nuclei became pycnotic and the cytoplasmic outlines quite ragged. Following the discontinuance of insulin, the beta cells regained their normal appearance. Alpha cells remained unchanged throughout the course of the experiments. Prompt reversal of changes which may occur

[37] Donath and Tanne: Arch. f. exp. Path., 119, 222, 1927. Werner and Monguio: Klin. Wchnschr., 12, 1, 748, 1933. Clausen: Kliniske Undersøgelser over Insulin resorptionens Paavirkelighed af Adrenalin, Pituitrin og Ephetonin, Dissertation, Copenhagen, 1934.
[38] Bischoff and Maxwell: Am. Jour. Physiol., 112, 172, 1935.
[39] Scott and Fisher: Jour. Clin. Invest., 17, 725, 1938.
[40] Haist: Physiol. Reviews, 24, 409, 1944.
[41] Haist, Ridout and Best: Am. Jour. Physiol., 126, 518, 1939.
[42] Haist, Campbell and Best: New England Jour. Med., 223, 607, 1940.
[43] Latta and Harvey: Anat. Rec., 82, 281, 1942.

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[21] ... Assn, *89*, 318, 1927. Power, Cragg ... 936

[22]

[23]

[24] ... Am Med Assn, *99*, 935, 1932

... and Technical Publications, London, ...

[29] Jensen Insulin Its Chemistry and Physiology, New York, The Commonwealth Fund, 1939

[30] Scott Loc cit, p 138 ... *9*, Boston, Little, Brown, 1956

... Klin d Univ München, München-

... Lancet, *205*, 777, 1923

... 371, 1925

...), 1930 Skouge and Schrumpf

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Insulin Content of the Pancreas.—Scott and Fisher[39] carried out analyses for insulin and zinc in the pancreases of 14 normal and 18 diabetic persons They found that, whereas there were on the average 1 7 units of insulin per gram of non-diabetic pancreas, the corresponding value for diabetic ... although not quite as striking, ... ntent, there being 0 14 mg of ... compared with 0 07 mg per gram of diabetic pancreas Haist[40] summarized the values obtained by ... s in different species ... eas are high for the ... the guinea pig (0 08 ... ht of the animal, the

Haist, Best and associates[41, 42] in a series of studies found that in rats, fasting, fat-feeding and the administration of insulin caused a reduction in the insulin content of the pancreas Continuing their work with dogs, they found that fasting, fat-feeding and the administration of insulin prevented the reduction in the insulin content of the pancreas which results from administration of anterior pituitary extract They concluded that in the studies both in the rat and the dog, the effects observed following the three procedures were due to resting the islets

Latta and Harvey[43] noted that when albino rats were subjected to repeated ... in the ... of secr ... volume ... in the ... beta cells the nuclei became pycnotic and the cytoplasmic outlines quite ragged Following the discontinuance of insulin, the beta cells regained their normal appearance Alpha cells remained unchanged throughout the course of the experiments Prompt reversal of changes which may occur

[37] Donath and Tanne Arch f exp Path *119* 222 1927 Werner and Mongino Klin Wchnschr, *12*, 1, 748 1933 Clausen Kliniske Undersøgelser over Insulin resorptionens Paavirkelighed af Adrenalin Pituitrin og Ephetonin Dissertation Copenhagen, 1934

[38] Bischoff and Maxwell Am Jour Physiol *114* 472 1935

[39] Scott and Fisher Jour Clin Invest *17* 725 1938

[40] Haist Physiol Reviews *24*, 409 1944

[41] Haist, Ridout and Best Am Jour Physiol *126*, 518, 1939

[42] Haist, Campbell and Best New England Jour Med, *223* 607 1940

[43] Latta and Harvey Anat Rec *82* 281 1942

as the result of fasting was evident in the studies of Foglia[44] with pancreas grafts from fasted dogs.

Insulin Content of the Blood.—It is obvious that if there were a simple, convenient method for measuring the insulin content of the blood, its use would aid in diagnosis, treatment and prognosis. Unfortunately, the development of such a method is fraught with great difficulties because of the tiny amount of insulin present. In an attempt to find a sensitive preparation, Eston and Rapp,[45] working in Best's laboratory at Toronto, used hypophysectomized, adrenalectomized mice as test animals. The blood sugar of the mice was determined before, and at thirty and sixty minutes after, the intraperitoneal injection of plasma to be tested for insulin content. Using this technique, they found a significant difference in hypoglycemic effect between the plasma of normal and that of depancreatized dogs. Similar studies were carried out in Australia and England by Bornstein[46,47] using alloxan-diabetic, hypophysectomized, adrenalectomized rats as sensitive test animals. The extent of fall of blood glucose of the rats following the injection of 1 ml of the patient's plasma was taken to indicate the amount of insulin present. From results obtained with known amounts of crystalline insulin, Bornstein regarded the sensitivity of the method to be in the range of 1/20,000 to 1/2000 of a unit (0.05 to 0.5 milliunit). From preliminary studies with human patients, Bornstein and co-workers[48,49] differentiated between two types of diabetes with and without available plasma insulin. Patients in the first group were characterized by hyperglycemia and glycosuria but no ketosis and were of the type whose condition may often be controlled without insulin if weight is lost. Those in the second group were characterized not only by hyperglycemia but also by an easy tendency to ketosis. Such patients require insulin in order to live.

More recently, methods have been developed for the determination of insulin-like activity in serum or plasma by measuring the glucose uptake by the isolated rat hemidiaphragm *in vitro*. Although this makes possible the detection of gross changes in insulin-like activity, the accuracy of the method is of low order, its sensitivity is not sufficiently great and reproducibility of results by different investigators is not of satisfactory degree. Fortunately, under the conditions used for the diaphragm technique, adipose tissue takes up glucose much more avidly. Using non-traumatized epididymal fat from the male rat, Martin,

0.01 milliunits per ml may be detected (a milliunit is 1/1000 of a unit). In Table 28 are given data collected by Dr. Martin from the literature together with representative values obtained by him and his co-workers.

[44] Foglia: Compt. rend. Soc. de biol., *127*, 694, 1938.
[45] Eston and Rapp: Rev. brasil. de biol., *8*, 367, 1948.
[46] Bornstein: Aust. Jour. exper. Biol. med. Sci., *28*, 87, 93, 1950.
[47] Bornstein and Trewhella: Jour. Endocrinology, *7*, 33, 1951.
[48] Bornstein and Lawrence: Brit. Med. Jour., *1*, 732, 1951.
[49] Bird and Bornstein: Lancet, *1*, 1111, 1957.

TABLE 28.—INSULIN BIOASSAY—CLINICAL DATA IN MAN
(Prepared by Dr Donald B Martin)

Author	Assay System	Normal* Levels in Blood: Fasting milliunits/ml †	Normal* Levels in Blood: After Glucose milliunits/ml †
Gellhorn[39]	*In vivo*—Adrenalectomized, hypophysectomized rats	—	0.2
Bornstein[41]	" " —Alloxan diabetic, adrenalectomized, hypophysectomized rats	0.1	0.2–0.4
Green[42]	*In vitro*—Glucose uptake by rat hemidiaphragm	0.05–0.1	—
Randle[43]	" " " " " " "	±1.0	10.0–20.0‡
Vallance-Owen[44]	" " " " " " "	0.03–0.08	0.06–0.8
Wright[45]	" " " " " " "	0.01–0.15	0.15–0.7
Martin *et al*[46]	" " Glucose uptake by rat adipose tissue	0.05–0.2	0.2–0.6

*Values found for diabetic patients are inconsistent, but in the hands of most workers, those for juvenile diabetics are near zero (or even inhibitory in the systems tested), and for the non-ketotic, maturity-onset diabetics are in the normal range

†Milliunits (1/1000 or 10^{-3} units) of insulin-like activity per ml of plasma or serum

‡The reason for these higher values is not clear

[39] Gellhorn *et al* Endocrinology, *29*, 137, 1941
[41] Bornstein Loc cit p 112
[42] Willebrands and Green Diabetes, *5*, 378, 1956
[43] Randle Brit Med Jour, *1*, 1237 1954
[44] Vallance-Owen *et al* Lancet, *1*, 68, 1954
[45] Wright Ibid *2*, 621, 1957
[46] Martin, Renold and Dagenais Presented at the Third Congress of the International Diabetes Federation, Düsseldorf, Germany, July 22, 1958

Insulin Requirement of Man.—In the past there was much speculation as to the amount of insulin required to maintain normal carbohydrate metabolism in man in the absence of the pancreas. Formerly, only estimates based on animal studies were possible; these varied from 50 to 200 or 300 units daily.[54] However, in recent years total pancreatectomy has been carried out in a sufficient number of patients to allow a good estimate as to the insulin requirement of the depancreatized man.[55–58] The experience of the Mayo Clinic with 4 patients was reported in 1946 by Waugh *et al.*[59] The daily insulin requirement in these patients was 26 to 40 units. In a paper published in 1951 Warren[60] of the Lahey Clinic reviewed the literature on total pancreatectomy, finding 24 patients who had been operated with a postoperative mortality of 45.8 per cent. Striking in these patients was the low insulin requirement of less than 50 units a day, an amount less than that needed by many diabetic patients. This is in keeping with the finding of Dragstedt, Allen and Smith[61] that the insulin requirement of partially depancreatized dogs is greater than that after total pancreatectomy. The experience bears out also the estimate of Bertram,[62] based on Holm's[63] experiments with depancreatized dogs, that a 60 kg. man with no insulin produced in his own body would require daily 7.8 units of insulin if fasting and 48 units if caloric needs were met exclusively by glucose.

The cause for the relatively low insulin requirement of the completely depancreatized man has naturally been the subject of much discussion. Possibilities suggested are: (*a*) decreased absorption of food associated with lack of normal pancreatic enzymes with lessening of the need for insulin. However, this factor can be largely ruled out by the addition of pancreatic extracts to the diet, (*b*) since in man total pancreatectomy involves removal of the duodenum, a portion of the stomach and in some cases the spleen, the absence of these organs may account for the difference.[64] There is no direct evidence to support this idea, (*c*) cells of the pancreas, presumably the alpha cells, elaborate not only a hypoglycemic principle, insulin, but also a hyperglycemic factor, glucagon.

Resistance to Insulin.—From time to time, since the introduction of insulin, reports have appeared regarding individuals with whom extraordinarily large amounts of insulin have been required in order to control the diabetic condition. Thus, in the patient of Levi and Friedman[64a] in whom diabetes was accompanied by chronic lymphatic leukemia, 76,195 units were administered in forty-seven days, on four successive days, the patient received 4000 units in each twenty-four hours. Such patients have been

[illegible] nology, 4, 194, 1944
[illegible]
[illegible] Surg., 119, 211, 1944
[illegible] g., Gynec. and Obst., 80, 252, 1945
[illegible] and Comfort: Proc. Staff Meet., Mayo Clinic, 21, 25, 1946
60 [illegible] 1951
61 [illegible] Med., 54, 292, 1943
62 [illegible] ed., p. 78, 1939
63 [illegible]
64 [illegible]
64a [illegible]

resistant to insulin unless a daily requirement of 200 or more units of insulin existed over a considerable period of time It goes without saying, however, that such a division of cases is purely arbitrary.

Excluding those patients who required huge amounts of insulin during diabetic acidosis or acute infections but returned to customary levels following recovery from these acute processes, some 30 patients have been seen in the Joslin Clinic whose insulin requirement over days, weeks or months of time has without adequate explanation remained at a level of 200 units a day or more

Our first patient who required extraordinarily large amounts of insulin, Case 6247, a physician, aged fifty-two years, reported by Root,[60] was observed in Boston in 1927 At this time the urine was not sugar-free with 100 units of insulin daily A few months later the insulin had to be increased until finally he was taking 1000 units of insulin a day in spite of which he died in coma At autopsy advanced hemochromatosis involving the pancreas, liver and heart, as well as the skin was found In this patient, it was assumed that hemochromatosis was responsible for the high insulin requirement

Our experience has been that in most patients the high insulin requirement falls over days, months or years to appreciably lower levels and in a considerable percentage of cases, the new insulin requirement which is set up is much the same as that present prior to the onset of the insulin resistance One of the most striking examples of this behavior is given in the following report of a patient for whom, despite studies which in 1939 seemed complete, no clue was gained as to the cause for the insulin resistance which lasted for at least one and one-half years

Case 15761, female was first seen on June 13 1937, at the age of forty The onset of diabetes had been in January, 1935 Her diabetic life had not been extraordinary up until about April 1, 1939 She had spent sixteen days at the Deaconess Hospital in January 1939, at that time her insulin requirement was 64 units of insulin daily On or about April 1 she noted that her urine tests for sugar were poor despite increases of insulin dosage ordinarily used Consequently she had increased the amount so that on the day before her admission on May 8 she had taken 502 units She spent three months in the hospital in the summer of 1939

[illegible]

to 100 units or less and in the five succeeding years the requirement has remained between 50 and 100 units With this patient as with certain others no cause for the remarkably high requirement for insulin was found It is true that this patient exhibited pronounced local skin responses to most varieties of insulin When last heard from August 1958 her diabetic condition was under good control on a diet

[60]Root New England Jour Med 201 1929

of C 199, P 85, P 104, and 52 units of insulin daily During recent years she has successfully gone through two surgical operations, one for removal of a nontoxic thyroid adenoma and the other for removal of a papilloma of the urinary bladder.

Among the 54 cases summarized by Smelo,[646] there were 18, or 33 per cent, in whom after intervals of two days to three years, the patient had regained his customary sensitivity to insulin. The accumulated experience of clinicians everywhere indicates clearly that it is vitally important in a literal sense to find that insulin dose, however large, which is necessary for the individual and to furnish it for as long as necessary. If this is done, barring complications in themselves fatal, there is justifiable hope that the insulin resistance through the passage of time and by control of diabetes will gradually disappear. From the standpoint of time required, Smelo estimates that not more than three years are required. It is interesting to

more than 5,000 units in twenty-four hours.

This patient, Mr. D K., Case 35695, was found to have a high insulin requirement in October 1949 Following admission to the New England Deaconess Hospital on January 7, 1950 the insulin dose was gradually increased until on January 17 and 18 he received 2300 units daily. On January 19 he was given 1250 units at 9.30 A M
The l
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and arteriolar nephrosclerosis

A most extraordinary patient is Mrs. H R , Case 50795, first seen on January 13, 1958, through the courtesy of Dr Paul L Barclay, Jr

This 55-year-old married woman with six children had developed diabetes in 1944 This had been well controlled by treatment with diet and insulin over the years About a year prior to her first visit to us she had increased fatigue, weight

[646] Smelo Proc Am Diabetes Assn , 8, 75, 1948

The problem as to the nature and cause of insulin resistance has been approached in various ways. Certain workers have attempted to classify patients into categories according to associated disease states. Thus, Smelo[66] grouped 54 patients with reference to the following basic factors: (1) The functional integrity and innate characteristics of the tissues which contribute sugar to and remove sugar from the blood. In this category Smelo listed 3 patients with hemochromatosis, 1 with recurrent jaundice and 1 with multiple liver infarcts; (2) cellular enzyme systems which catalyze the chain of reactions involved in the formation and disappearance of glucose. In this group he placed 2 patients with lipodystrophy and cirrhosis of the liver and 1 case of defective hepatic glycogenesis; (3) the regulators of these tissue functions, the endocrine system hormones and the central nervous system. Under this heading were 18 patients who were considered to have an insufficiency of insulin either because of delayed absorption [illegible]
logic ma [illegible]
tion or [illegible]
7 cases w [illegible]
as seen [illegible]
brain cy [illegible]
this attempt at classification, only 33 cases were taken care of, leaving 21 patients in whom no feature was apparent to explain the high requirement for insulin.

Stetten[64] has listed the ways in which antagonism to insulin of the serum or plasma of certain insulin-resistant individuals has been demonstrated, as

follows: (1) Decrease in the hypoglycemic effect of insulin in the intact animal (mice, rabbits, etc.) when mixed with antagonist serum,[64i,64f,64g] (2) reduction of response to insulin by the isolated rat diaphragm in the presence of antagonist serum;[64h] (3) decreased binding of insulin-I^{131} by the rat diaphragm when antagonist serum is present;[64i] (4) alteration in the electrophoretic mobility of insulin-I^{131} when dissolved in antagonist serum.[64i]

Some years ago Lerman,[64k] Lowell[64l] and others suggested that insulin resistance might be related to the development of antibodies with the degree of resistance paralleling their concentration. That, despite the small size of its molecule, insulin is definitely though weakly antigenic, is now well recognized [illegible]

ciated with the gamma globulin fraction of the serum. However, Berson and Yalow[64m] in electrophoresis studies demonstrated that the insulin-antibody complex migrates in the "inter-gamma-beta zone," *i e*, in the region *between the fastest gamma globulins and slowest beta globulins.* Berson and Yalow[64m] suggest that the temporary increase in insulin requirement which frequently accompanies acute infections may be due in part to non-specific stimulation of the rate of insulin antibody production.

In a study of sera obtained on admission from patients in diabetic keto-*acidosis, Field and Stetten[64n] found evidence of insulin antagonism in* samples from those patients who required large amounts of insulin (more than 250 units) in the first 24 hours. This antagonist was short-lived and apparently not an antibody since it migrated electrophorectically chiefly in the alpha globulin range

In certain of our patients there have been demonstrated positive skin tests, precipitins, passive transfer antibodies and neutralizing antibodies. Howeve [illegible]
allergy [illegible]
patient [illegible]
to be several factors involved

Patients requiring large doses of insulin present a great practical problem in treatment Obviously the use of the usual U40 and U80 strengths of insulin would necessitate the injection of large volumes of liquid day after day Fortunately, U100 and even U500 strengths of crystalline insulin are

[64o]Stetten Diabetes, 5, 321, 1956
[illegible]

[illegible] 1955
[illegible], 1952
[illegible] ndocrin and Metab, *15*, 861, 1955
[64j] Berson, Yalow, Bauman, Rothschild and Newerly Jour Clin Invest, *35*, 170, 1956
[64k]Lerman Proc Am Diab Assn, *8*, 107, 1948 See also Lerman Am Jour Med Sci, *207*, 354, 1944
[64l]Lowell Jour Clin Invest, *23*, 225, 233, 1944 Proc Soc Exper Biol and Med, *50*, 167, 1942
[64m]Berson and Yalow Jour Clin Invest, *36*, 642, 1957
[64n]Field and Stetten Amer Jour Med, *21*, 339, 1956

daily before breakfast and to have the effect last for twelve, eighteen or even twenty-four hours

laboratory studies (2) Special studies to rule out infections, hyperthyroid-

may be considered in those patients in whom an immunologic mechanism with exaggerated antibody formation appears to be involved However, the administration of steroids is not without danger in those patients in whom infection is present (5) In any case, insulin should be given freely to the point of tolerance regardless of the size of dose concerned Clinical experience suggests that consistent attempts to meet fully the insulin requirement, however great, are of aid in "breaking" the resistance

Methods of Administration of Insulin. – Insulin is a protein and as such is broken down by the digestive juices of the stomach and intestine When this happens, potency is lost
to control diabetes when taken orally
and advertisements of such products
journals To date insulin administered parenterally is the only agent available which affords treatment specific for diabetes

Although attempts to date to secure absorption of insulin from the gastrointestinal tract have been unsuccessful from a practical point of view, much has been done in the way of investigation with this in mind Murlin[64] and his associates for years carried out studies with the object of finding some way in which to protect the insulin molecule from the destructive action of the digestive juices and to facilitate its absorption through the intestinal wall These and other workers found that in general there are three classes of substances which are effective (1) alkyl derivatives of resorcinol (2) glycol derivatives, and (3) sapogenins. Favorable effects seem to depend in part on surface action (the resorcinols and the sapogenins lower surface tension) and in part on the presence of hydrophylic and hydrophobic groups Calcium reduces intestinal permeability, consequently agents such as sodium hexametaphosphate which combine with calcium, favor absorption In a report[65] of the Rochester workers published in

[64] Driver and Murlin Am Jour Physiol 127 480, 1939
[65] Murlin Gibbs Romansky Steinhausen and Truax Jour Clin Invest, 19, 709 1940

September, 1940, describing their results with an insulin-hexylresorcinol mixture given to 20 human patients with diabetes, they characterized their findings as "only mildly encouraging."

Wilson, Sappington and Salter[67] have shown that the inactivation of insulin by proteolytic enzymes *in vitro* may be reversed in whole or in part. Under the conditions of their experiments, the oral administration of insulin preparations caused hypoglycemic coma or convulsions in mice within two hours after administration. The effective oral dose for "undigested" insulin was about 90 times, and for "digested" insulin about 45 times, the subcutaneous dose. Iron salts increased the effectiveness of insulin preparations given orally. Cutting and Robson[68] treated 10 ambulatory diabetic patients with insulin orally, using quinine sulfate and insulin in capsules which were insoluble in gastric juice. Quinine was selected with the idea that it might allow absorption by inhibiting enzymatic action and by local effect on the cell surface. The results were not encouraging.

Insulin is effective when injected subcutaneously, intravenously, intraperitoneally or into the liver or spleen.[69] Absorption from the rectum, vagina and skin is incomplete and uncertain. Spirig and Valette[70] stated, however, that preliminary treatment of the skin with petroleum ether permits a definite and rapid absorption of insulin by both rabbit and man. It has been reported that intratracheal application produces hypolgycemia though not as regularly as do hypodermic injections. It is stated that effective absorption may take place from the respiratory epithelium when a nebulized[71] or aerosolized[72] insulin solution is inhaled. The literature regarding unusual modes of administration was summarized by Jenson[73] and in an editorial in the British Medical Journal.[74]

The administration of insulin through the skin by jet injection ("Hypospray") is entirely possible[74a] and has been used in certain special situations but at present is not practical for routine use.

Rate of Absorption of Insulin.—The rate of absorption of three types of insulin injected subcutaneously was studied by Reiner and co-workers,[75] by using radioactive insulin preparations. As might be anticipated, the rate of absorption was most rapid in the case of unmodified insulin, next with globin (zinc) insulin and slowest with protamine zinc insulin. The differences in rates of absorption were correlated with the differences in intensity of hypoglycemic action of the preparations studied.

Root and associates[76] injected insulin-4-iodo-azobenzene containing radioactive iodine subcutaneously into selected diabetic patients and normal controls and studied the rate of absorption. This occurred rapidly during the first two hours and more slowly thereafter in both normal controls and

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[74a] ..., 185, 1950

[75] ... Jour Pharm and Exper Therap, *78*, 352,

[76] Root, Irvine, Evans, Reiner and Carpenter Jour Am Med Assn, *124*, 84, 1944

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Radoslav Test.—In the Radoslav test the effect of a definite amount of insulin on the capillary blood sugar of a fasting subject is determined over a period of four [illegible]
capillary blood [illegible]
counter-regulat[illegible]
curve tells nothing regarding the degree of sugar uptake by the tissues, workers in Falta's clinic[79, 80] elaborated the Radoslav experiment by the simultaneous determination of the venous blood-sugar curve The size of the plotted surface between the capillary and venous blood-sugar curves was used to give an idea of the strength of counter-regulatory factors in the tissues

Himsworth Test [81]—In this procedure a fasting subject is given glucose by mouth and insulin by vein simultaneously and capillary blood samples are taken at frequent intervals for the following ninety minutes In insulin-sensitive persons the blood-sugar rise which would ordinarily follow the giving of glucose is wholly or partly prevented by the insulin, whereas in insulin insensitive subjects, the injection of insulin appears to have had little or no effect.

The test of Himsworth is valid in that all individuals, diabetic or non-diabetic, can be divided in two groups, those who are insulin-sensitive and those who are insulin-insensitive However, in our own work[82] in which some 30 patients of varying ages and severity of diabetes were carefully studied, it became apparent that the results often could not be correlated with clinical facts so that from a practical standpoint such tests were of no

77 Radoslav Wien Arch f inn Med 8 305 1924
78 MacBryde Arch Int Med, 52 932 1933 Jour Clin Invest 15 577 1936
79 Falta Renaler und Insularer Diabetes Berlin and Vienna Urban & Schwarzenberg p 7, 1939
80 Dexaness and Uiberrak Klin Wchnschr 19 347 1940 Ibid 19 966 1940
81 Himsworth Lancet, 1, 127, 1936
82 Marble, Smith and Fernald Unpublished data

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76 Root, Irvine, Evans, Reiner and Carpenter Jour Am Med Assn, *124*, 84, 1944

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RADOSLAV TEST —In the Radoslav test the effect of a definite amount of insulin on the capillary blood sugar of a fasting subject is determined over a period of four or five hours It is assumed that a large decrease in the capillary blood sugar shows a weak, and a small decrease a strong, hepatic counter-regulatory mechanism Since, however, the capillary blood-sugar curve tells nothing regarding the degree of sugar uptake by the tissues, workers in Falta's clinic[79, 80] elaborated the Radoslav experiment by the simultaneous determination of the venous blood-sugar curve The size of the plotted surface between the capillary and venous blood-sugar curves was used to give an idea of the strength of counter-regulatory factors in the tissues

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78 MacBryde Arch Int Med 52, 932, 1933 Jour Clin Invest, *15*, 577, 1936
79 Falta Renaler und Insularer Diabetes Berlin and Vienna, Urban & Schwarzenberg, p 7, 1939
80 Deraneas and Uiberrak Klin Wchnschr *19* 347 1940, Ibid, *19*, 366, 1940
81 Himsworth Lancet *1* 127 1936
82 Marble, Smith and Fernald Unpublished data

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[74] Editorial [illegible]
[74a] Perkin *et al* Proc Amer Diabetes Assn, *10*, 185, 1950
[75] Reiner, Lang, Irvine, Peacock and Evans Jour Pharm and Exper Therap, *78* 352, 1943
[76] Root, Irvine, Evans, Reiner and Carpenter: Jour Am Med Assn, *124*, 84, 1944

Chen, Anderson and Maze[90] found birds (canary, pigeon, duck and rooster) to be less sensitive to insulin than mammals (mouse, rabbit and dog). The duck was about 30 times as tolerant of insulin as the rabbit Among the birds studied, the rooster was the least sensitive and failed to develop convulsions even with lethal doses of insulin In further studies,[91] horned owls were likewise found insensitive to insulin and did not develop convulsions even with extreme prolonged hypoglycemia Intravenous injections of 1000 to 4000 units per kilogram caused death in only 4 of 11 [illegible]

[illegible]

persons require large doses of insulin to produce the desired effect [92]

B. TESTS OF PANCREATIC FUNCTION

Various special tests have been devised in order to evaluate the functional efficiency of the pancreas These may be summarized as follows:

(*a*) The Hamman-Hirschman (Staub-Traugott) Effect.—Hamman and Hirschman[93] and later Staub[94] and Traugott[95] showed that the administration of sugar in two divided portions separated by a definite space of time (thirty to ninety minutes) produces a different effect on the blood sugar in the normal as compared with the diabetic In the normal healthy [illegible]

[illegible]

more nearly does the Staub-Traugott curve approach the normal

These relationships are brought out even more clearly if one gives, as Grote[96] suggested, at intervals of every half hour, 10 grams of glucose by mouth Such administration causes the blood sugar of the diabetic, at least for a certain period, to continue to rise With the normal person, however, after the second or third dose of sugar, the peak of the blood-sugar curve is reached Then follows a fall and a more or less horizontal course from then on Grote concluded that with diabetic patients who are not receiving injected insulin it is best to give food, particularly carbohydrate, at intervals throughout the day rather than concentrating it in three meals

(*b*) German authors have written a good deal concerning the value of the determination of the blood-sugar curve throughout an entire day ("Tages-

[90] Chen Anderson and Maze Jour Pharm *84*, 74 1945
[91] Scott and Chen Fed Proc 5 201, 1946
[92] Rivers and Elliott Jour Lab and Clin Med, *29* 55, 1944
[93] Hamman and Hirschman Johns Hopkins Hosp Bull *30* 306 1919
[94] Staub Biochem Ztschr *118* 93 1921
[95] Traugott Klin Wchnschr, *1* 892 1922
[96] Grote Ergebn. d ges Med *18* 301 1933

persons with lesser degrees of impaired carbohydrate tolerance cannot safely be relied upon to differentiate so-called hepatic storage insufficiency from true diabetes mellitus; (2) patients with persistent hyperglycemia and glycosuria should be treated as diabetic. If liver disease is present, both conditions should be treated simultaneously.

TABLE 29—COMPOSITE VALUES FOR SERUM PHOSPHORUS AND POTASSIUM FOLLOWING THE INTRAVENOUS ADMINISTRATION OF GLUCOSE

(Adapted from Gundersen, Bradley and Marble[103])

Type of Subject	No. of Cases	Serum Phosphorus Maximum Fall: Range per cent	Average per cent	Serum Potassium Maximum Change: Range m eq /l	Average m eq /l
Normal	21	35–4	19	0 to −1.1	−0.33
Borderline diabetic	4	29–13	22	−0.4 to −0.8	−0.53
Diabetic	23	32–5	18	+0.25 to −1.0	−0.32

C. THE BLOOD SUGAR

[illegible]

Reports upon percentages of sugar in the blood vary according to the method used in the determination. The values just cited refer to "true glucose" as determined by the Somogyi-Nelson procedure.[104] By excluding the non-glucose-reducing substances, this method gives lower values for sugar than do older procedures. This non-glucose fraction, consisting chiefly of glutathione and ergothioneine but also of cysteine, creatinine and undetermined substances, has copper reducing ability equivalent to that of about 20 mg. (range, 10 to 30 mg.) of glucose per 100 cc. of blood. However, the figure is variable and unpredictable, ranging in reported figures from zero to 78 mg. per cent.[105] Mosenthal and Barry found values exceeding 30 mg. per cent in 27 per cent of 200 blood sugar determinations (in 50 consecutive glucose tolerance tests) in one study[105] and in 38 per cent of 200 determinations in another series.[106] Likewise Haunz and Keranen[107] found that 39 per cent of 100 subjects had non-glucose reducing substances exceeding 30 mg. per cent. In fact, the average value for 34 normal persons was 26 mg. and for 66 diabetic patients, 30.6 mg. per cent. For a discussion of "true glucose" methods, see page 200.

For many years we have made extensive use of capillary blood. This is of especial help in dealing with children and with patients from whom it is desirable to take blood for examination at frequent intervals. It must be noted, however, that the use of capillary methods requires that not only

[104] Nelson: Jour. Biol. Chem., 153, 375, 1944.
[105] Mosenthal and Barry: Ann. Int. Med., 33, 1175, 1950.
[106] Mosenthal and Barry: Am. Jour. Digest. Dis., 13, 160, 1946.
[107] Haunz and Keranen: Proc. Amer. Diabetes Assn., 10, 200, 1950.

blutzuckerkurve" or "Tagesprofil") in giving a good idea of the tolerance of the patient and the severity of the diabetic condition.[97]

(c) Among others, Depisch and Hasenohrl, in Falta's Clinic,[98] ascribed the hypoglycemic phase which follows the overloading of the body with sugar as in a tolerance test, to overstimulation of the pancreas and the overproduction of insulin. This view has been attacked by Soskin[99] Depisch and Hasenohrl determined both the capillary and venous blood

capillary. In the diabetic this does not properly take place This abnormality may be corrected in the diabetic by the administration of an appropriate dose of insulin.

(d) Blood Phosphorus and Potassium Following Glucose.—It is generally agreed that following the administration of glucose to a normal subject, the serum (or plasma) phosphorus falls. This is true particularly if the glucose is given intravenously.[100] The fall in phosphorus presumably reflects withdrawal of this element for use in the phosphorylation process. Many believe that this decrease depends upon the activity of insulin, since it does not take place in the pancreatectomized animal or in the severe diabetic Patients with mild diabetes may exhibit a fall in blood phosphorus similar to that seen in normal individuals, so that the test is not useful for diagnosis in borderline situations. Certain workers have regarded the fall in phosphorus as an index of peripheral utilization of glucose and on this basis have attempted to use that obtained to differentiate between true diabetes mellitus and so-called "liver diabetes," in which hepatic dysfunction is held responsible for the hyperglycemia and glycosuria observed. Forsham and Thorn[101] report that in "liver diabetes" a normal fall in blood phosphorus is obtained Wilson, Frawley, Forsham and Thorn[102] have also stated that the behavior of the serum potassium during the course of an intravenous glucose tolerance test is helpful in the accurate diagnosis of diabetes They reported that in a series of diabetics the blood potassium fell to a greater extent than was the case in normal subjects

This whole problem was considered anew by Gundersen, Bradley and Marble[103] who studied 11 normal subjects and 41 patients by means of intravenous glucose tolerance tests with concomitant determinations of serum inorganic phosphorus and serum potassium An evaluation of liver function was made on the basis of history, physical findings and a series of liver function tests Their results are summarized in Table 29. From their data they drew the following conclusions: (1) The behavior of the serum phosphorus and potassium following the giving of glucose intravenously to

[97] Schone and Zimmer Klin Wchnschr, *14*, 1672, 1935
[98] Falta Loc cit p 151
…, 1934
…2, 1956
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…etes Assn, *10*, 25, 1950
…*250*, 547, 1954

of true glucose in venous blood following the ingestion of glucose furnish more dependable data on which to evaluate carbohydrate tolerance than do determinations of either the capillary blood sugar or the venous blood sugar by the Folin-Wu or similar procedure. Because of variable and unpredictable capillary-venous differences, all would agree with Langner and Fies[109] that if only capillary blood-sugar values are obtained, the interpretation of glucose tolerance curves is frequently difficult.

Factors Affecting the Blood Sugar.—Endocrine influences affecting the

Aside from endocrine factors and from the giving of food or glucose there are many influences which may cause a rise in the sugar content of the blood. Often such influences arise from situations of stress with release of

of rats swiftly to under 22° C. by plunging them into ice water. This led to a transient rise of the blood sugar, to an almost complete disappearance of the liver glycogen and to a decrease of nearly 50 per cent in the muscle glycogen. Creatinuria of two to three days' duration resulted.

l sugar and

the intake of fluid has no constant influence on the blood-sugar level

ether narcosis

Larson[116] found that neither pentobarbital nor evipal in the doses he used had any appreciable effect on the blood-sugar level of rats or on hypoglycemia induced by insulin. Oelkers and Schultze[117] found that cocaine produced a rise in blood sugar in normal individuals and that in rabbits

fore, in the presence of pyloric obstruction or when for any reason the

[109] Langner and Fies. Am. Jour. Clin. Path., *12*, 93, 1942.
[110] Long. Diabetes, *1*, 3, 1952.
[111] Samaras. Ztschr. f. d. ges. exper. Med., *106*, 510, 1939.
[112] Kirstein and Bromberg. Jour. Lab. and Clin. Med., *25*, 7, 1939.
[113] Meyer. Ztschr. f. d. ges. exper. Med., *106*, 409, 1939.
[114] McKittrick and Root. Diabetic Surgery, Philadelphia, Lea & Febiger, p. 76, 1928.
[115] Lauber and Bersin. Klin. Wchnschr., *7*, 232, 1939.
[116] Larson. Fed. Proc., 5, 189, 1946.
[117] Oelkers and Schultze. Klin. Wchnschr., *25*, 871, 1938.
[118] Maddock, Trimble and Carey. Jour. Biol. Chem., *103*, 285, 1933.

the laboratory technician, but also the person who withdraws the blood, be a careful worker, trained in the manipulation involved. This is not so much the case when venous blood is used, for then the main requisite is to get a sufficient quantity of blood into a suitable container. It may then later be examined in the laboratory by a trained technician.

In diabetes the increase in the percentage of sugar in the blood varies widely, depending upon the severity of the disease, upon the previous treatment and upon complicating conditions. Thus, the blood sugar in the postabsorptive state may be normal, although a common diabetic value is that of two times the normal, namely, 160-200 mg. per 100 cc. In patients with severe diabetes, particularly in children, the fasting blood sugar may be 250-300 mg. per cent or higher. High fasting values are almost invariably accompanied by marked glycosuria. In diabetic coma, values from 300 to 600 mg. per cent are the rule, but at times one finds values of 1000 mg. per cent or over. In our series of 945 consecutive cases of diabetic coma there were 45 such cases; 34 recovered and 11 died. Among our patients the highest blood sugar with recovery was 2250 mg. per cent.

In the normal individual, within the first thirty to sixty minutes following the intake of food, the blood sugar rises and then falls to normal within two hours. It is difficult to say how high the postprandial blood sugar may rise without being abnormal. Consequently it is helpful to establish definite standards in order to make the matter of diagnosis systematic and to avoid confusion. It is our rule to regard a blood sugar of 150 mg per
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arbitrarily accepted 180 mg per 100 cc. as the lowest value on which to make the diagnosis of diabetes. When diabetes and hyperthyroidism coexist, then it is helpful to raise the postprandial value for venous blood from 150 to 180 mg per 100 cc, thus excluding certain thyrotoxic individuals in whom slight hyperglycemia may not indicate true diabetes but rather abnormally rapid absorption of sugar from the gastro-intestinal tract or perhaps only a temporary lowering of carbohydrate tolerance (idiothyroid diabetes).

Sugar in Venous an
the concentration of
fasting state is essent
rises on the average
blood sugar. In 200 consecutive determinations (in 50 glucose tolerance tests), Mosenthal[108] found the difference to vary widely from −19 to +124 mg. This arteriovenous difference reflects the oxidation or storage of glucose in the tissues. In the untreated diabetic the arterial and the venous blood-sugar curve following a meal or following the giving of sugar may be almost identical, indicating that very little sugar is taken up by the tissues. With the giving of insulin, however, and control of the diabetic state, an arteriovenous difference approaching the normal may be achieved.

From their experience Mosenthal and Barry conclude that determinations

108 Mosenthal. Loc. cit., p. 155

the urine, has been carefully investigated Campbell, Osgood and Haskins[128] found the renal threshold for "true sugar" to vary from 99 to 228 mg. per cent, 80 per cent of the cases having values that ranged from 140 to 190 mg per cent. However, there is so much variation from individual to individual

glucose" technique and capillary blood, they found that usually glycosuria occurred at a level of about 200 mg. per cent.

It is well to point out that, although the concept of a "renal threshold"

one may cite the elevated "renal threshold" found in certain cases of diabetes with concomitant nephritis and uremia in which, because of glomerular damage, glycosuria may not occur despite levels of blood sugar of 300 to 400 mg per 100 cc [129] Finally, in renal glycosuria is seen the effect of the third factor, that of impaired efficiency of tubular reabsorption

It is at times desirable to know the approximate level of the "renal threshold" A suitable procedure is to withhold food in the morning and to take specimens of urine and arterial (capillary) blood at half-hourly intervals If with the passage of time, it becomes apparent that the blood sugar will not fall low enough to permit disappearance of glycosuria, then a dose of crystalline insulin, usually 10 or 12 units, may be given and the collection of blood and urine specimens at half-hourly intervals continued The level of blood sugar at the time at which the urinary sugar clears up represents the approximate threshold In patients in whom the threshold is not at such low levels but above 100 mg per 100 cc, it is possible to determine it by tests of the urine and capillary blood for sugar at fifteen to thirty minute intervals following the giving of 50 to 100 gm of glucose

Rarely is catheterization justifiable for the sake of the test alone, but more accurate data are possible thereby

Corcoran[130] has described another method by which may be found the approximate level of blood sugar at which glycosuria will begin This is calculated from the "maximum glucose reabsorptive capacity" of the tu-

[128] Campbell, Osgood and Haskins Arch Int Med, 50, 952, 1932
[11] Mosenthal and Barry Loc cit, p 155
[129] Marble Med Clin North America, 21, 427, 1937
[130] Corcoran Cleveland Clinic Quart, 15, 186, 1948

emptying of the stomach is interfered with, food or liquid given by mouth may not be absorbed. This is of practical importance to the physician who is treating an unconscious patient suffering from hypoglycemia due to insulin. Under such conditions one often obtains little or no relief from orange juice or other carbohydrate-containing solutions given by mouth and only after glucose has been injected intravenously does recovery take place One must, however, call attention to the work of Morrison, Shay, Ravdin, and Cahoon[119] who concluded that glucose is absorbed from the stomach to some extent when introduced in concentrations over 40 per cent. Absorption was slight when solutions of 15 per cent glucose were introduced and negligible or absent when concentrations below 7 per cent were used. These findings suggest that in severe hypoglycemia in which delay in gastric emptying is suspected, the use of corn syrup by mouth might be more efficacious than that of fruit juices. On the other hand, Goldfarb and Golden[120] found that in patients with hypoglycemic coma due to insulin, the ingestion of glucose in 5 per cent solution produced a more rapid recovery than when a 30 per cent solution was administered.

[illegible]

of absorption and variations in certain other factors, such as the concentration of dextrose ingested, the length of the absorption period, the weight of the animals used and the excitement occasioned by experimentation.

The problem as to whether or not glucose administered rectally is absorbed has been studied by various workers, with variable results Carpenter's[122] results suggested that from 55 to 90 per cent might be absorbed with the greater part of the absorption taking place within the first two hours. Scott and Zweighaft[123] were unable to demonstrate a rise in the blood-sugar curve as a result of administering dextrose in retention enemata. Absorption increases, of course, if by reverse peristalsis the sugar solution is carried through the ileocecal valve into the lower ileum Eberling[124] found that glucose solutions were absorbed very slowly when placed in the entire colon of a dog, and that 10 per cent solutions were absorbed only slightly better than isotonic solutions He observed, however, that with hypoglycemia prevailing, the absorption of glucose from the colon can be as rapid as that from a low ileal loop of a non-insulinized dog Duncan[125] states that the patient in hypoglycemia may absorb considerable glucose from solutions administered rectally He recommends in emergencies the giving by slow drip of 20 gm of glucose or corn syrup dissolved in 8 ounces of warm water

Renal Threshold for Glucose. The glucose or renal threshold, that is, the percentage level of sugar in the blood above which sugar appears in

[119] Morrison, Shay, Ravdin and Cahoon Proc Soc Exper Biol and Med, 41, 131, 1939

[illegible] se and Levulose.

W [illegible]

[illegible])51, p 160

Wishnofsky and Kane[137] carried out tolerance tests on 21 diabetics, comparing the effect of 100 grams of dextrose with 90 grams of starch in the form of potato, barley, rice and bread (90 grams of starch on hydrolysis yield 100 grams of dextrose). They found that the blood sugar curves which resulted did not differ significantly.

Sugar Tolerance Tests.—(*a*) Type and Amount of Sugar.—Although

is undoubtedly safest, but even then one must regard sugar tolerance tests as often unsatisfactory. In order for results to be valid for the diagnosis of diabetes, the glucose tolerance test must be done under carefully controlled conditions. Otherwise various factors may cause a normal person to exhibit a diabetic type of response.[138] The subject must have been on an

ordinary clinical work the tolerance test, if carefully done and intelligently evaluated, is consistent enough to be of great value in the diagnosis of diabetes.[140] For a comprehensive discussion of methods and evaluation of sugar tolerance tests the paper by Blotner[141] should be consulted.

Because of the abundance of literature with the easy availability of comparable values, it is preferable to give glucose orally in dosage of 100 grams to adults. To adults under 100 pounds in weight a suitable test dose is 50 grams. To children, 2.0 gm. per kg. body weight is given (roughly, 1 gm. per pound of body weight). It has been stated that tolerance curves satisfactory for diagnostic purposes can be obtained as readily with the use of 50 grams of glucose as with 100 grams, even in adults of average size. This is undoubtedly true to a large extent. However, in the normal person, the larger amount of sugar may be expected to prolong the hyperglycemia obtained and in the diabetic, both a higher level and a prolongation of the hyperglycemia may be produced.[142] In our practice it is the custom to take urine and blood samples fasting and at one-half, one hour and two hours after the giving of the sugar. Occasionally it is worth while to prolong the test to three hours. Blood may be taken either from a vein

[138] Adlersberg and Porges: Klin. Wchnschr., 5, 1451, 1926.

[139] Sweeney: Arch. Int. Med., 40, 818, 1927. See also Sweeney, Tunnell and Tunnell: Am. Jour. Clin. Path., 14, 437, 1944.

... 9, 515, 1935.

... 7, 1943.

... ocrin., 2, 431, 1942.

... 1941.

... Assn. Life Ins. Med. Dir. Am., 18, 252, 1931. Hansen: Acta med. Scand., Supp. IV, 1, 1923.

bules as determined from the urea clearance and concurrent blood and urine sugar estimations.

There ar [illegible] diabetes [illegible] as in norm[illegible] may be high or low, but in general the threshold in diabetics tends to be higher than in normals This is true particularly in elderly diabetics and especially in the pre[illegible] nephritis; Steinitz[130] [illegible] explained on the ba[illegible] article by Marble.[131]

Food Tolerance Tests.—Since even in the diabetic the fasting blood sugar may be normal, various food and sugar tolerance tests have been devised to aid in diagnosis Food tolerance tests, and particularly sugar tolerance tests, are often fallacious.[132] The results may be as unfair to the patient as to the doctor or insurance company. The previous diet of the subject is a definite factor and will be discussed at some length in the next section If an individual lives upon a rigid, low-carbohydrate diet for some days and a liberal carbohydrate meal is then taken, hyperglycemia may develop to such an extent that a diagnosis of diabetes is warranted. This phenomenon has been emphasized by Odin,[133] Malmros,[134] Adlersberg and Porges[135] and Sweeney.[136] The last-named writer found that there was a delayed postprandial rise in blood sugar in hydrated animals, a definite decrease in tolerance after a fat diet and starvation, a slight decrease in tolerance on a protein diet, but an increase in tolerance on a carbohydrate diet.

TABLE 30 —FOOD TOLERANCE TEST

Time	*Urine Sugar, per cent*	*Blood sugar, per cent*
Four hours after breakfast	*0 1*	*0 10*
Lunch Baked beans, potato, 1½ rolls, apple pie ice cream		
One hour after lunch	trace	0 23
One and a half hours after lunch	3 0	0 27

Every meal is a food tolerance test A simple way in which to determine whether or not a patient has diabetes is to make the examination without previous notice *after a dinner of meat, potato, bread, pie, and coffee with sugar* The urine should be essentially free from sugar before, at one hour and at two hours, after the meal (See Table 30) It can be tested immediately, and if sugar-free, the probabilities are that the patient does not have diabetes, but for more conclusive evidence simultaneous tests for sugar in blood and urine should be performed If the results are still inconclusive, a glucose tolerance test should be carried out

130 Steinitz Jour Clin Invest, *19*, 299, 1940
131 Marble Loc cit, p 159
132 Meyers and McKean Am Jour Clin Path, *6*, 299, 1935 Leyton Brit Med Jour, *2*, 536, 1935
133 Odin Acta med Scand, Suppl *18*, pp 1–573, 1927
134 Malmros Zentralbl f inn Med, *48*, 214, 1927

As the result of a study in which one-dose and two-dose tolerance tests were carried out in the same subjects, Goto[148] concluded that in the two-dose procedure the Staub effect appeared to lack significance

Duncan[149] abandoned the Exton-Rose procedure because (1) there is a high incidence of inconclusiveness regarding diagnosis in doubtful cases, (2) the test does not give an accurate estimate of a subject's ability to dis-

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value does not exceed 120 mg per cent, although the diagnosis of diabetes would in the average case not be justifiable unless a value of 150 mg per cent or more was attained. Within two hours the blood sugar should have fallen to 100 mg per 100 cc. or lower.

In normal persons the blood sugar rises less after the mid-day meal than after breakfast if the interval between the two meals is three to five hours This difference is not constant in normals and still less so in diabetics

high or lasted so long, and to this extent indicated improvement of the patient Sakaguchi[151] explained the above phenomena on the basis that at breakfast-time glycogen formation by the liver is at a low ebb The indication, therefore, would be not only to make the carbohydrate at breakfast less than at the other meals, but to precede breakfast with a small amount of carbohydrate Gray's[152] experience with divided meals in our clinic was a practical confirmation of these observations

(*c*) Factors Influencing the Sugar-tolerance Curve.[153]—1 *Previous Diet* – As has been mentioned earlier, the sugar-tolerance curve is greatly influenced by the previous diet [154] Thus, with normal individuals or animals who have either been starved[155] or kept on a low-carbohydrate

[148] Goto Metabolism, 4, 323, 1935
[149] Duncan Page 86 Loc cit, p 158
[150] Maclean Modern Methods in the Diagnosis and Treatment of Glycosuria and Diabetes, London Constable & Co, 1922
[151] Sakaguchi Mitt d med Fakultät d Kais Universität zu Tokyo, *20*, 439, 1918
[152] Gray Boston Med and Surg Jour, *186*, 763, 1922
[153] John Southern Med Jour, *36*, 624, 1943
[154] Chabanier Lobo-Onell and Lelu Presse med 39, 1133, 1931 Boller and Uebcrrack Klin Wchnschr, *11*, 511, 1932 Sweeney Arch Int Med, *40*, 818, 1927 Himsworth Jour Physiol *81*, 29, 1924 Malmros Acta med Scand, Suppl 27, 1928
[155] Aubertin Lacoste, Sorie and Castagnon Compt rend Soc de biol, *120*, 1107, 1935

or from the ear or finger. If capillary blood is used, due regard must be given for the higher values which are usually secured on such samples Whereas we ordinarily make the diagnosis of diabetes if a venous blood sugar rises to a height of 150 mg per 100 cc. or more, we do not feel that the diagnosis of diabetes is justified unless the capillary blood sugar rises at least to 180 mg per 100 cc. Unless the results are unequivocally abnormal, we prefer
values because of
venous difference.
in an individual w

TABLE 30a —BLOOD SUGAR LEVELS (VENOUS) DIAGNOSTIC OF DIABETES DURING GLUCOSE TOLERANCE TESTS

	"True Glucose" (Somogyi-Nelson) mg per 100 cc.	Folin-Wu Values mg per 100 cc
Fasting	110	130
Peak Value	150	170
2-hour Value	110	130

These values for both venous and capillary blood are lower than those chosen by certain other clinicians for the diagnosis of diabetes Indeed, certain authorities pay little or no attention to the height of the tolerance curve, but classify a curve as a normal one if at the end of two hours the blood-sugar value has returned to 100 mg. per 100 cc. or lower. We consider this latter point to be of great value, but we believe that one cannot disregard the height to which the curve goes In borderline cases it is well to be conservative and to repeat the test on a later occasion.

Exton-Rose Test—The Hamman-Hirschman effect (see page 153) has been utilized by some workers, among them Exton and Rose[143] as means of diagnosis Patients are given 50 grams of glucose after the fasting blood sugar has been determined At the end of one-half hour a second blood

second whereas in the non-diabetic person the third blood sugar will be lower or no more than 10 mg (later modified to permit somewhat greater rise) higher than the second This one-hour, two-dose procedure was designed principally for life insurance work to minimize inconvenience to the subject and was carried out usually with capillary blood Although the test has been used considerably, it has not found general acceptance and seems to have few or no advantages and certain disadvantages over the standard test[144–147]

143 Exton and Rose Am Jour Clin Path, 4, 381, 1934
144 Matthews, Magath and Berkson Jour Am Med Assn, 113, 1531, 1939
145 Wayburn and Gray Am Jour Med Sci, 204, 823, 1942
146 Langner, Romansky and Rohn Am Jour Med Sci, 212, 466, 1946
147 Mosenthal and Barry Am J Digest Dis, 18, 168, 1951

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[148] Goto Metabolism *4* 323 1955
[149] Duncan Page 86, Loc cit , p 158
[150] Maclean Modern Methods in the Diagnosis and Treatment of Glycosuria and Diabetes London Constable & Co , 1922
[151] Sakaguchi Mitt d med Fakultat d Kais Universitat zu Tokyo, *20*, 439, 1918
[152] Gray Boston Med and Surg Jour *186*, 763, 1922
[153] John Southern Med Jour *36* 624 1943
[154] Chabanier, Lobo-Onell and Lelu Presse méd , *39*, 1133, 1931 Boller and Ueberrack Klin Wchnschr *11* 511 1932 Sweeney Arch Int Med , *40*, 818, 1927 Himsworth Jour Physiol *81* 29, 1924 Malmros Acta med Scand Suppl 27, 1928
[155] Aubertin, Lacoste Sore and Castagnon Compt rend Soc de biol , *120*, 1107, 1935

diet or on a diet high in fat, a diabetic type of curve may be obtained following the giving of the usual dose of dextrose.

Conn[156] advises that for at least three days before a test is done a diet providing at least 300 grams of carbohydrate, 80 grams of protein, and calories sufficient for maintenance be used. Although there is general agreement that a sugar tolerance test should not be done in individuals who have been taking starvation or near-starvation diets, doubt has been cast on the necessity for as much as 300 grams of carbohydrate daily. From their experience Irving and Wang[157] concluded that probably 100 grams daily are adequate and that there is no necessity for augmenting the normal diet of the adequately nourished patient before the performance of a glucose tolerance test. Likewise Wilkerson and co-workers[158] found in controlled studies among prisoners that amounts of carbohydrate in the previous diet much less than 300 grams daily prevented the securing of falsely abnormal glucose tolerance tests. Available evidence would appear to suggest that, from a practical standpoint, valid results may be expected in a glucose tolerance test if the individual has been taking at least 150 grams of carbohydrate daily (together with adequate amounts of protein and calories) during the three days just prior to the test.

If doses of dextrose are given to normal men or animals on successive days the rise of the blood-sugar curve becomes less and less day by day, or if on the same day successive doses of glucose are given, the second curve reaches its peak at a lower level than the first and the third lower than the second, and so on. With rabbits it is possible eventually to produce severe hypoglycemia with convulsions by this method.[159] Ellis[160] found that hourly doses of insulin and glucose produced a temporary improvement in the carbohydrate tolerance of severe diabetics. When given in excess of the ability of the diabetic patient to oxidize it, carbohydrate is of no benefit.

A common explanation for the above findings[161] is that the carbohydrate given stimulates the pancreas so as to produce more insulin. Another explanation has been offered by Soskin and co-workers[162] who, from studies of depancreatized dogs receiving a constant intravenous injection of glucose and insulin, concluded that the pancreas is not essential for the production of a normal dextrose-tolerance curve. On the other hand, the presence of a normal liver was necessary. They postulate that the normal liver, as one of its responses to administered dextrose, decreases the output of blood sugar which it has been supplying from its own stores. They maintain that the hypoglycemia which follows the cessation of prolonged sugar administration does not depend upon an increased mobilizatoin of insulin from the pancreas, but rather represents another aspect of a homeostatic liver mechanism.[163]

[156] Conn. Am Jour Med Sci, *199*, 555, 1940
[157] Irving and Wang. Glasgow Med Jour, *35*, 275, 1954
[158] Wilkerson and others. Personal communication
[159] Lennox. Jour Biol Chem, *73*, 237, 1927 Jour Clin Invest, *4*, 331, 1927
[160] Ellis. Quart Jour Med, *3*, 10, 137, 1934
[161] Sweeney. Loc cit, p
[162] Soskin, Allweiss and Co[illegible] Soskin and Allweiss. Ibid, *110*, 4, 1934 Ibid, *114*, 648, 1936
[163] Soskin, Essex, Herrick and Mann. Ibid, *124*, 558, 1938

Best and Taylor[164] and Ricketts,[165] while recognizing the significance of the experiments of Soskin and co-workers, cite as evidence of chemical control of insulin liberation through action of dextrose on the pancreas the finding that the injection of small amounts of dextrose into the artery supplying a pancreas grafted into the neck of a depancreatized dog[166] or into the pancreatic artery in a decerebrate cat[167] causes a prompt lowering of blood sugar, whereas (in the decerebrate animal) the effect was not obtained when the splenic or portal vein was used.

Infections and Toxemias.—With a diabetic an infection, even a nonfebrile coryza, may exert an effect upon sugar tolerance. The same tendency is evident in non-diabetic individuals, who, however, have a greater ability to compensate. Hence, under no circumstances should diagnostic significance of final nature be attached to blood sugar values unless the element of an infection is absolutely excluded at the time of the test. Therefore, it is desirable to record the body temperature of patients routinely at the beginning and end of a sugar tolerance test.

Much has been written regarding this effect of infections and toxemias on carbohydrate tolerance. Relevant papers are those of Corkill,[168] Long and Downie,[169] Schmidt, Eastland and Burns,[170] Strauss,[171] Williams and Dick,[172] Brems and Nissen,[173] and Soskin and Mirsky.[174]

Insulin.—Previous insulin administration has been shown to cause a temporary loss of tolerance for carbohydrate in normal men[175] and animals.[176] Consequently, no sugar tolerance test for diagnostic purposes should be carried out unless the subject has received no insulin for a definite period of time, say three days.

Physical Inactivity.—Blotner[177] compared the glucose tolerance of normal active adults and children with that of 86 non-diabetic patients, 70 adults and 16 children, who had been confined to bed for periods of time ranging from one month to thirteen years because of various pathologic conditions. He found the sugar tolerance diminished in those patients who had been bedfast for considerable periods. In some who later became ambulatory, the tolerance returned to normal. Although various disease conditions may in themselves lower sugar tolerance, Blotner concluded that in his studies hypertension, vascular disease, obesity and infection were not responsible for the abnormalities noted.

[164] Best and Taylor. Physiological Basis of Medical Practice, Baltimore: Williams and Wilkins, 5th ed. P. 578, 1950.
[165] [illegible]
[illegible] I., *100*, 140, 142, 1929.
[illegible]
[illegible] 66, 1934.
[illegible]
[172] Williams and Dick. Arch. Int. Med., [illegible]
[173] Brems and Nissen. Ugesk. f. Laeger, *94*, 1203, 1932; Abst., Jour. Am. Med. Assn., *100*, 706, 1933.
[174] Soskin and Mirsky. Am. Jour. Physiol., *112*, 649, 1935.
[175] Wilder, Smith and Sandiford. Ann. Int. Med., *6*, 724, 1932. Blotner. Arch. Int. Med., *53*, 153, 1934. Clark, Gibson and Paul. Jour. Lab. and Clin. Med., *20*, 1008, 1935. Rosenbaum, Dekruif and Lavietes. Jour. Clin. Invest., *23*, 45, 1914.
[176] Opdyke. Proc. Soc. Exper. Biol. and Med., *57*, 119, 1944.
[177] Blotner. Arch. Int. Med., *75*, 39, 1945.

diet or on a diet high in fat, a diabetic type of curve may be obtained following the giving of the usual dose of dextrose.

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, 331, 1927

Soskin and All-
Ibid., 114, 648,
1936

[163] Soskin, Essex, Herrick and Mann Ibid., 124, 558, 1938

and diseases of the liver, of the pituitary and of the adrenals are the most common

In a study of 1100 glucose-tolerance tests, John[158] found that diabetic curves were shown in 40 per cent or more of cases having the following conditions: diabetic history in the family, obesity, hyperthyroidism, acro-

and Page [159]

That disturbed gastro-intestinal absorption plays an important role in abnormal glucose tolerance curves which may be obtained with organic or functional gastro-intestinal disorders is suggested by the data of Goldner and Haerem [160] These workers subjected dogs to resections of various parts of the gastro-intestinal tract and then carried out glucose tolerance tests Following the administration of glucose intravenously, the curves were

Watson,[191] who emphasized the point that in situations in which there is rapid emptying of the stomach and consequent rapid absorption of sugar from the intestine, a sharp, early peak is seen in the glucose tolerance curve

at times sufficient to suggest the diagnosis of diabetes Nissen and Spencer[196] found that 57 per cent of 222 arthritic patients showed abnormal tolerance curves Serial tests covering one to nine years on a group of 33 patients showed, however, that even a markedly low sugar tolerance did not *per se* indicate a future diabetic

Shay and associates[197] carried out three-hour glucose tolerance tests in

glucose tolerance curves in advancing years is related to the higher incidence of anacidity in those age groups

In an analysis of 500 obese subjects Embleton[198] found abnormal glucose

[158] John Endocrinology *13* 388 1929
[159] Berkovitz and Page Ann Int Med *20* 239 1944
[160] Goldner and Haerem Proc Soc Exper Biol and Med *52* 186, 1943
[191] Alway and Watson Am J Digest Dis *17* 50 1950
[192] Test Nichols Landau Ricketts, and Loughead Am Jour Med Sci, *231*, 69, 1956
[193] Pemberton Cajori and Crouter Jour Am Med Assn 85 1793 1925
[194] O Hare Am Jour Med Sci *160* 366 1920
[195] John Ann Clin Med 5 340 1926
[196] Nissen and Spencer New England Jour Med *210* 13 1934
[197] Shay, Gershon and Fels Am Jour Dig Dis 5 4 1938
[198] Embleton Brit Med Jour 2 739 1938

5. *Age.*—Th
Spence,[178] I
tolerance te ... decrease as age advances.

The higher rise and slower fall in blood sugar in old age after the administration of glucose were confirmed by Marshall[181] who studied 50 men aged sixty-five to ninety-four years with an average age of seventy-two years Of the 28 healthy subjects, only 6, or 21 per cent, showed normal ("normal adult" and "flat" types) blood sugar curves The remaining 22 men all

... sugar of 200 mg. per cent or higher after the giving of 50 grams of glucose. In these 18 cases, only 7 showed glycosuria during the tolerance test and in 3 of the 7 instances only traces of sugar were exhibited. The con-

... decades starting with that of thirty to forty years. Using 50 grams of glucose, the following average results were obtained for the capillary blood sugar:

Age	*Before*	*½ hr*	*1 hr*	*1½ hrs*	*2 hrs*	*2½ hrs*
30–40	105	181	174	153	150	140
40–50	120	192	207	165	155	152
50–60	146	225	218	195	166	155
60–70	145	225	238	215	205	185
70–80	115	175	190	185	165	130

John[183] found abnormal glucose tolerance curves (venous blood samples used) in 18 per cent of 102 children ...
per cent c
varying d
that among 52 children and 337 adults with glycosuria, 33 and 37 per cent respectively showed a diabetic type of tolerance curve.

Blotner's[184] findings, previously referred to, suggest that at least part of the decreased sugar tolerance found in elderly persons may be due to relative inactivity.

6 *Diseases and Abnormal States Other Than Diabetes.*—Conditions other than diabetes are at times accompanied by elevated blood-sugar percentages or diminished tolerance for carbohydrate. Of these, hypertension, nephritis,[185] pregnancy, hyperthyroidism,[186] hypothyroidism, fractures[187]

[178] Spence Quart Jour Med, *14*, 314, 1921
[179] Hale-White and Payne Ibid, *19*, 393, 1926
[180] Jessop Annual Rep M Res Council of Ireland, p 13, 1949
[181] Marshall Quart Jour Med, *24*, 257, 1931
[182] Porter and Langley Lancet, *2*, 947, 1926
[183] John Endocrinology, *18*, 75, 1934
[184] Blotner Loc cit, p 165
[185] Oefelin Klin Wchnschr, *15*, 407, 1936
[186] John Jour Am Med Assn, 99, 620, 1932, Jour Clin Endocrin, *2*, 264, 1942
[187] Sachar, Walker and Whittico Arch Surg, *60*, 837, 1950

individuals went, they observed the hyperglycemic effect only when the blood sugar was below 0.13 per cent and the respiratory quotient below 0.85. More recently, Scheer[209] reported that smoking produced a change in the blood sugar level in 85 per cent of men. He found most curves to have a biphasic pattern. The response started usually between one and three minutes after the beginning of smoking and seldom lasted more than fifty minutes.

Contrary [illegible] one cigarett [illegible] quotient. [illegible] increased 5 to 15 per cent and suggested, therefore, that subjects for basal metabolic rate determination not smoke on the morning of the test before it is made.

Fluctuations in Blood Glucose.—Anderson *et al.*[210a] found that in the postabsorptive state, the blood level is constantly changing. They reported that when successive determinations were made at two-minute intervals in 100 unselected persons, significant variations (mean value, 22.2 mg. per 100 ml. of blood) occurred from reading to reading in 81 per cent of the subjects. The authors consider that this constant oscillation reflects the homeostatic mechanism by which relative constancy of the blood glucose is maintained.

Glycogen in Blood.—The concentration of glycogen in the blood was determined by Brummer[211] in 125 individuals. In both healthy persons and in those with certain chronic diseases including diabetes, the amounts found were very small and were not increased by the administration of insulin or the ingestion of glucose. The only high values noted were in 21 patients with pneumonia, this increase was thought possibly to be due to the presence of polysaccharides of bacterial origin.

Wagner[212] found the average glycogen content of normal human blood to be 5.5 mg. per cent. Plasma, red blood corpuscles and blood platelets did not contain measurable amounts. The glycogen content of wet white blood cells of normal persons ranged from 0.17 to 0.67 per cent. In polycythemia concentrations up to 1.64 per cent, and in glycogen storage (von Gierke's) disease[212] up to 3.05 per cent were found. The polymorphonuclear leucocyte was the only type of cell in the peripheral blood which contained glycogen. The breakdown of glycogen in leucocytes was shown to occur not as the result of diastatic enzyme activity but to be catalyzed by a phosphorylase.[213]

Using histochemical methods, Mancini[214] observed a marked increase in the glycogen of the neutrophiles of human diabetics when hyperglycemia, glycosuria and ketonuria were present.

[209] Scheer. Ztschr. f. d. ges. exper. Med. *111*: 356, 1943.
[210] Dill, Edwards and Forbes. Am. Jour. Physiol., *109*: 118, 1934.
[210a] Anderson, Hillman, van Elk and Perfetto. Amer. Jour. Clin. Nutrition *4*: 673, 1956.
[211] Brummer. Acta med. Scand. *114*: 373, 1943.
[212] Wagner. Amer. Jour. Dis. Child. *73*: 559, 1947.
[213] Wagner. Arch. Biochem. *26*: 123, 1950.
[214] Mancini. Rev. Soc. Argent. Biol. *25*: 190, 1949.

tolerance curves in 70 per cent of the males but in only 35 per cent of the females. This sex difference was found chiefly in the older age groups. He,

most cases normal in the early stages of obesity but steadily diminished after obesity had persisted for several years

Extreme Hyperglycemia.—It is remarkable that the human body can at times withstand successfully marked variations in the sugar content of the blood. The patient of Dillon and Dyer,[200] a colored woman, aged twenty-one years, entered the Philadelphia General Hospital in diabetic coma with a blood sugar of 1.85 per cent. Recovery took place with the giving of 810 units of insulin during the first twenty-four hours Dillon and Dyer reported also 15 other cases from the same hospital with blood sugar values on admission of 1 per cent or more. Five of the 16 recovered. The highest percentage observed in our own series, 2250 mg per cent, was in a patient with diabetic coma who survived [201] We have had in all, 45 cases with values of 1 per cent or above; of these 34 recovered. High blood sugar values in cases resulting fatally have been reported by others Lawrence's[202] case had a value of 2.06 per cent, Argy's[203] 1.71 per cent, Pitfield's[204] 1 7 per cent, and Olmsted's[205] 1.4 per cent See also page 355

The blood glucose of the patient of Meyer and Salt[206] was 2.1 per cent after the administration of 660 units of insulin and 320 Gm of glucose in 16 hours Recovery took place

Effect of Nicotine Upon the Blood Sugar.—Lundberg and Thyselius-Lundberg[207] made detailed studies regarding the effect of tobacco-smoking on the blood sugar of both normal and diabetic individuals By taking *samples at intervals of one minute they found that immediately after the* beginning of smoking the blood sugar rose sharply The highest value obtained was as much as 50 per cent above the initial value and was usually reached during the smoking of two cigarettes, one after the other, at an ordinary rate The subsequent fall to normal was accomplished usually within one-half hour With diabetic patients, a more marked hyperglycemic effect was seen than in normal persons, and this was even more [illegible] excreting sugar and acetone In common [illegible] scribed the

3. Hemochromatosis
4. Surgical removal

II. Selective destruction of insular tissue.

1. Hyaline infiltration
2. Fibrosis
3. Toxic injury with lymphocytic infiltration
4. Hydropic change
5. Reduction in beta cells due to unknown causes

III. Inadequate blood supply

1. Arteriosclerosis

I. DESTRUCTION OF PANCREATIC TISSUE.—1 *Pancreatitis*—There are increasing numbers of reports in the literature, not only of temporary glycosuria and disturbance of glucose tolerance in the course of acute pancreatitis, but also of a relatively high incidence of diabetes in patients with chronic pancreatitis, with or without demonstrable calculi. Fibrosis of the pancreas, both inter- and intralobular, is quite common in diabetes. It occurred to some degree in nearly half of our series of 881 diabetic autopsies, and in 74 of these was regarded as severe. Vartiainen[2] found gross fibrosis of the pancreas 30 times in a series of 166 diabetics and not at all in a control series of the same number. The mere finding of fibrosis in a pancreas does not, of course, necessarily imply insulin deficiency, especially since the islands of Langerhans have a remarkable faculty of surviving in the midst of dense fibrous tissue. (This situation may be reproduced experimentally by ligation of the pancreatic duct system in a dog, in which case the acinar tissue is eventually replaced by fibrous tissue, but the islets, at least the majority of them, survive.)

2. *Malignant Disease*.—In a series of 132 cases of cancer associated with diabetes and studied at autopsy at the New England Deaconess Hospital 19, or 14 per cent, were primary in the pancreas. This is to be compared with figures of from 2.5 to 4.8 per cent for the incidence of carcinoma of the pancreas in nondiabetics. When the 19 cases were studied from the point of view of symptomatology, it appeared that in over half the cases the symptoms of cancer either antedated the symptoms of diabetes or occurred simultaneously with them.[3] These data suggest that destruction of the pancreas by cancer is a reasonably important cause of diabetes. Bell[4] has apparently reached a similar conclusion, although he interprets his data somewhat differently. In this connection recent papers stressing the value of the glucose tolerance test in the diagnosis of carcinoma of the pancreas may be cited. However, as noted by Marble,[5] the suitability of cancer patients of any type for the glucose tolerance test may be questioned.

3. *Hemochromatosis*.—"Bronze diabetes" has, of course, been known for many years. The essential lesion seems to be the deposition of iron pigment

[2] Vartiainen. Acta med scand 118 538, 1944
[3] Warren and LeCompte. Loc cit, p. 170
[4] Bell. Am Jour Path 13 499, 1937
[5] Marble. New England Jour Med 211 339, 1934

Chapter 6

THE PATHOLOGY OF DIABETES

SHIELDS WARREN, M.D. AND PHILIP M. LECOMPTE, M.D.

THE changes that may be found at autopsy on a diabetic patient are so varied, heterogeneous, and apparently unrelated that it is difficult to discuss them in a coherent manner. For convenience they will be grouped under (*a*) lesions of possible etiological significance, both pancreatic and extrapancreatic, (*b*) manifestations of disturbed carbohydrate metabolism, (*c*) manifestations of disturbed fat metabolism, and (*d*) the so-called complications of diabetes. It should be emphasized that this grouping is quite arbitrary, especially since one may hypothesize, on the basis of modern histochemical methods, that practically all the structural changes in diabetes may be the result of disturbed carbohydrate (polysaccharide) metabolism. (*See page 186*).

For a more detailed description of the lesions, with more extensive references and illustrations, the monograph by Warren and LeCompte[1] may be consulted

A LESIONS OF POSSIBLE ETIOLOGICAL SIGNIFICANCE

Pancreatic Lesions.—*Since it is probable that a sustained diabetic* state depends upon a disparity between the organism's need for insulin and the ability of the islets of Langerhans to supply that need, it is natural to look to the pancreas for evidence of an inadequate supply of insulin In the past the search for such structural change has often been disappointing, and it may be safely stated that from one-fourth to one-half or even more, of all cases of diabetes, *when studied by routine methods*, show no changes in the pancreas extensive enough to constitute a convincing cause of insulin deficiency. As noted below, newer differential staining methods, as well as new techniques for estimating the volume of the "islet organ," have shed light on this problem

Anatomical causes of insulin deficiency may be listed as follows

I Destruction of pancreatic tissue (both insular and acinar).
- 1 Pancreatitis
  - a Acute
  - b Chronic (with or without calculi)
- 2 Malignant disease
  - a Primary
  - b Metastatic

[1] Warren and LeCompte The Pathology of Diabetes Mellitus, Philadelphia, Lea & Febiger, 3d ed, 1952

points out, the amount of hyalinization is not necessarily related to the severity of the diabetes, and it is possible that it represents an associated phenomenon or even a result of the diabetes.

The pathogenesis is quite obscure. It appears to be an intercellular deposit. Much has been made in recent literature of the fact that the hyaline substance often (but not always) gives the staining reactions of amyloid. It has therefore been postulated that the substance is actually amyloid or something akin to it ("paramyloid"). This hypothesis, however, only raises new questions, since the chemistry and histochemistry of amyloid, which itself probably represents a group of related substances rather than a single entity, have not been well worked out. Fat may be present.[11a]

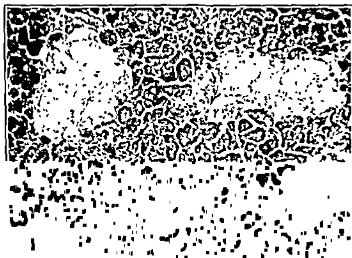


FIG. 14. Hyalinization of islands of Langerhans. This is an unusually severe case. Note two essentially normal arterioles in lower center. × 125.

The theory that hyaline change of the islands is really a capillary sclerosis, representing an extension from the arterioles, is not widely held but has recently been put forth by Moschcowitz.[15, 16] It is true that many cases of extensive hyaline involvement of the islands also show marked arteriolar sclerosis and the age incidence would favor this theory. However, the most severe case of hyalinization that we have seen showed almost complete absence of arteriolar involvement. (Fig. 14.) This was a male of forty-three who also had pulmonary tuberculosis.

2. *Fibrosis.* This becomes apparent with the presence of a definite fibrous capsule around the island and the invasion of the interior by fibroblasts. Slight fibrosis is more common than marked, in contrast to hyalinization. In all, 24 per cent of the pancreases in our series showed some

[11a] Wilson. Personal Communication.
[15] Moschcowitz. Ann. int. Med., 34, 1137, 1951.
[16] Moschcowitz. Arch. Path., 61, 136, 1956.

in various organs with resulting fibrosis. Although the liver is most severely involved, the pancreas may be the seat of pigment deposition directly in the islands of Langerhans as well as in the acinar and interstitial tissue.[6,7] In fact, the predilection of the pigment for the beta cells is remarkable.[7] Although the etiology of the disturbance in iron metabolism is still in doubt in most cases, interest has been recently turning to excess loading of the body with iron, as by multiple transfusions (so-called "exogenous hemochromatosis").[8]

Regardless of its fundamental pathogenesis, the disease is an interesting one in that it provides a clear example of production of diabetes by gradual destruction of the pancreas by a known agent. In some of these cases, evidence of attempted regeneration of islands has been observed.[9] Bell[10] doubts that the diabetes is due to damage to the islets. This is a point of view which we do not accept. Probably actual counts of beta and alpha cells should be done to settle this question.

4 *Surgical Removal.*—Several cases of total pancreatectomy in man with survival for periods of weeks to months are now in the literature. Such cases are interesting in having an insulin requirement of around 40 units per day, *i.e.*, less than many spontaneous cases of diabetes. The possible rôles played by the malnutrition consequent to loss of the external secretion of the pancreas or by glucagon secretion by the alpha cells in influencing the insulin requirement are unknown. It does not follow that this is a "mild" diabetes.[11]

II SELECTIVE DESTRUCTION OF INSULAR TISSUE.—1. *Hyaline Infiltration.*—Hyalinization of the islands of Langerhans, even though not specific for diabetes, has usually been regarded as the most typical lesion of the disease. It consists of the deposition of a hyaline material, apparently beginning beneath the basement membrane of the capillaries, and extending in some cases to obliterate the entire island. Its distribution is notoriously "spotty," some islands being usually found uninvolved in the same pancreas in which others show severe involvement.

The reported incidence of the lesion varies, depending probably in part on the care exerted in looking for it and in part on the criteria used to recognize it. In the series at the New England Deaconess Hospital it was found in 333 of 811 cases, or 41 per cent.[12] In spite of the fact that the classical case of Opie[13] was a girl of seventeen, the lesion is much more common in the older age groups. Thus, in the series referred to above, only 6.8 per cent of cases up to forty years of age showed the change, while 45.3 per cent of cases over forty were found to have it.

The fact that this lesion can be readily seen with routine stains has probably led to its being given undue importance in the past. As Bell[14]

, 590, 1951
th., *32*, 631, 1950
1955
115, 1925

[14] Bell Diabetes, [illegible]

largely because one hardly ever has the opportunity to do a post-mortem examination on a case of diabetes which is both newly discovered and untreated. Also, the issue is confused by the fact that hydropic change may be imitated by post-mortem alterations in the pancreas However, the change does occur in the human, and may be demonstrated in an occasional case in which, presumably, the surviving beta cells are under continuing "strain" due to the persistent action of the inciting agent, whatever it may be, or due perhaps simply to persistence of the diabetic state

Of great interest is the recent demonstration by Toreson[20] that many cases of hydropic change actually represent glycogen infiltration This finding is all the more surprising in view of the rather intensive study of the lesion by various workers since the classical observations of Allen However, Toreson's slides are convincing, and we have been able to repeat many of his observations For instance the islets from the rabbit pancreas illustrated in Figure 15 were shown by appropriate methods to contain abundant masses of glycogen in the cytoplasm of the vacuolated cells Demonstration of glycogen in the human pancreas is more difficult, probably due to the post-mortem change, but can be accomplished in occasional cases Also, it appears to be true that a transitory form of hydropic change which does not contain glycogen can be produced in rats by certain experimental procedures (starvation or insulin followed by re-feeding)[21]

Toreson's findings are, of course, of great theoretical interest, especially [illegible]

[illegible] gen in the cytoplasm of the beta cells, and interest centers mainly on means [illegible] ie have been [illegible] o prevent or [illegible] small doses of insulin, even in the presence of continuing hyperglycemia They, therefore, raise the question of whether hypoinsulinemia, rather than hyperglycemia, may not be the effective stimulus which leads to the deposit

Lazarus and Volk,[23] on the basis of studies on the effect of cortisone in rabbits, find that the glycogen appears first in the ducts and later in the islets, and therefore conclude that it is not necessarily indicative of "strain" but may be a part of the peculiar and bizarre deposits of glycogen found in various tissues in diabetes (see below p 180)

5 *Reduction in Number of Beta Cells Due to Unknown Causes* It has been generally agreed that at least a third of all cases of diabetes show islands of Langerhans which are apparently normal when studied by the

[20] Toreson Am Jour Path [illegible] 327 1951
[21] Nerenberg Arch Path [illegible] 75 1953
[22] Duff and Toreson Endocrinology [illegible] 298 1951
[23] Lazarus and Volk Diabetes [illegible] 15 1958

degree of this process. Except for cases of obvious chronic pancreatitis, with fibrosis of acinar tissue as well, the cause is not clear. Hartroft[17] emphasizes what he calls reduplication of the capillary basement membrane of the islets, presumably early fibrosis, as a useful criterion for the diagnosis of diabetes.

3. *Toxic Injury with Lymphocytic Infiltration.*—This is a rare lesion, found usually in children or young adults with diabetes of sudden onset.[17a] The cells of the islands appear to be the seat of gradual necrosis, with

"overstrain." However, it is more likely that hydropic degeneration is the characteristic morphological manifestation of "strain" (see next section).

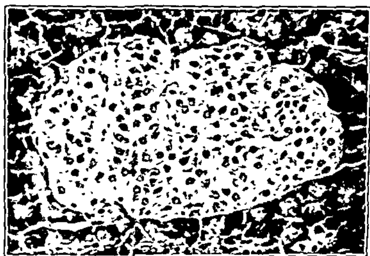


FIG 15.—Hydropic change in island of Langerhans in rabbit made hyperglycemic with large doses of cortisone × 140

4. *Hydropic Change.*—This vacuolated appearance of the beta cells of the islands of Langerhans has been recognized for nearly sixty years. Allen,[19] in his early experiments in diabetes, laid particular stress upon it. His statement that "it offers the only proved example of anatomical breakdown of cells due to overstimulation of an internal secretory function" is probably still true, although one may question whether the word "breakdown" is entirely appropriate, since the lesion has been shown to be reversible.

[17] Hartroft Proc Am Diab Assn, *10*, 46, 1950
[17a] LeCompte Arch Path *66*, 450, 1958
[18] von Meyenburg Schweiz Med Wchnschr, *21*, 554, 1940
[19] Allen Jour Metab Res, *1*, 5 1922

Recently, considerable controversy has arisen over the technical fickleness of the Gros-Schultze method and also over the question of whether it, or in fact any silver impregnation method, can be relied upon to stain all the alpha cells, and only the alpha cells.[30] On the one hand Ferner, Feyrter and Terbrüggen[31] continue to uphold the virtual specificity of the Gros-Schultze method, while on the other hand other authors (unfortunately usually using *other* methods of impregnation) maintain with equal vigor that some beta cells are also impregnated[32, 33] or that not all the alpha cells take the stain.[34]

In such a situation there has been a natural tendency to turn to the granule stains devised by the late Dr. Gomori.[35, 36] There have been two recent major studies[33, 37] of fairly large series of diabetic pancreases in which considerable effort has been made to arrive at an estimate of the total mass of beta and alpha cells in the pancreas. Such a determination would obviously be of greater value than the *ratio* of beta to alpha cells, which only indicates the relative proportions of the cell types. Maclean and Ogilvie,[37] using Gomori's chrome alum hematoxylin and phloxin stain and a painstaking quantitative method, have found a fairly consistent reduction in estimated total weight of islet tissue and of beta and alpha cells in a series of diabetic pancreases. The reduction was most marked in the juvenile or "growth-onset" type and least striking in the middle-aged, "maturity-onset" type. They found a remarkably good correlation between their estimates for weight of beta cells and the figures of Wrenshall *et al.*[38] for insulin content of diabetic pancreases at different age levels. They also found an increase in the mean size of islets with age in diabetics but not in non-diabetics. This they interpret as suggesting a possible pituitary influence. Their work has added more confirmation to the growing impression that the extent of granulation of the beta cells is closely correlated with the extractable insulin in a pancreas,[39] and that these granules represent either a form of stored insulin or a precursor of it.[40] Further important evidence has been provided by Barnett's histochemical method for insulin.[41] A possible role of zinc in the storage of insulin in the beta cells is still to be evaluated.[42, 43]

One corollary of the assumption that the beta granules represent stored insulin has been the use of modern staining methods to study the effect of the new oral sulfonylurea drugs on the islets of Langerhans.[44, 45]

[30] Creutzfeldt. Beitr. z. path. Anat. *113*, 133, 1953.
[31] Ferner, Feyrter and Terbrüggen. Virchows Arch. 326, 22, 1954.
[32] Creutzfeldt and Theodossiou. Beitr. z. path. Anat. *117*, 245, 1957.
[33] Gepts. Ann. d. l. Soc. Roy. Sci. Med. et Nat. Brux. *10*, 5, 1957.
[34] Volk, Goldner and Frank-Crowley. Metab. 4, 494, 1955.
[35] Gomori. Am. Jour. Path. *17*, 395, 1941.
[36] Gomori. Am. Jour. Clin. Path. *20*, 665, 1950.
[37] Maclean and Ogilvie. Diabetes 4, 367, 1955.
[38] Wrenshall, Bogoch and Ritchie. Ibid. *1*, 87, 1952.
[39] Hartroft and Wrenshall. Ibid. , 1, 1955.
[40] Lazarow. Ibid. *6*, 222, 1957.
[41] Barnett, Marshall and Seligman. Endocrinology, 57, 419, 1955.
[42] Maske. Diabetes, *6*, 335, 1957.
[43] Vogt. Acta path. et microbiol. Scand. *41*, 381, 1957.
[44] Loubatières. Diabetes, *6*, 408, 1957.
[45] Volk and Lazarus. Ibid., 7, 125, 1958.

usual histological methods. In recent years, in several papers in the European literature, it has been suggested that with proper staining methods a definite decrease in the ratio of beta to alpha cells can be demonstrated in most cases of diabetes. Most of these workers have used the Gros-Schultze method, which was popularized by Ferner [24] (see Figure 16). This technique, which unfortunately works well only on frozen or celloidin sections, consists essentially in exposure of the sections to silver nitrate for several hours, reducing in formalin, then treating with an ammoniacal silver solution, which apparently stains the alpha cells of the islets and scattered cells in the acinar tissue and in the ducts. These cells that are blackened by the silver are called collectively "silver cells." In his earlier papers Ferner held that



FIG. 16. Gros-Schultze stain of normal pancreas showing two islands of Langerhans with black "silver cells." Frozen section. × 250.

all of them, including the alpha cells, represented immature or unripe elements which had the property of being transformed into beta cells. More recently he has modified this view in recognition of the new evidence that the alpha cells may have the function of producing glucagon, and now suggests that there is a balance or an antagonism between the beta and alpha cells which is disturbed in diabetes[24,25]. He appears to hold that a consistent relative increase in "silver" cells can be demonstrated in diabetes, and has received some support in this view [26,27,28]. However, there has been a wide disparity in the normal beta to alpha ratio according to various authors. Ferner 5:1, Hess 9:1, Terbruggen 4:1, Gomori[29] 3:2 to 9:1.

[24] Ferner. Das Inselsystem des Pankreas. Stuttgart, Geo. Thieme, 1952.
[25] Ferner. Am. Jour. Digest. Dis., *20*: 301, 1953.
[26] Hess. Schweiz. Ztschr. f. Path. u. Bakt., *6*: 46, 1945.
[27] Terbruggen. Klin. Wchnschr., *24-25*: 434, 1947.
[28] Leyrer. Über die peripheren endokrinen (parakrinen) Drüsen des Menschen, Wien-Düsseldorf, Wm. Maudrich, 1953.
[29] Gomori. Personal communication.

sugar[58, 59, 60] or a significant part in the pathogenesis of diabetes.[61, 62, 62a, 63] The degranulation and atrophy of acinar tissue produced in dogs and rats by glucagon[64] is unexplained.

It is likely that the chief hope for the future in the morphological investigation of the islands of Langerhans lies in the electron microscope[65, 66].

IV. Inadequate Blood Supply.—Atherosclerosis or, more likely, arteriolar sclerosis of the pancreatic vessels has been proposed from time to time as an etiologic factor leading to fibrosis or hyalinization of the islets. The most recent proponent of this point of view is Moschcowitz[66a] (see above under discussion of hyalinization of islets). We have not been convinced that vascular disease *per se* is an important factor—as noted above, severe hyaline change or fibrosis may occur without severe vascular disease, and relatively few of the pancreases in our series showed marked arteriosclerosis in the pancreas. Functional limitation of blood supply, as by arteriolar spasm, is conceivable but has not been demonstrated.

Extrapancreatic Lesions.—Lesions of possible etiological importance in organs other than the pancreas are rare. They may be grouped under (*a*) endocrine, (*b*) obesity, (*c*) neurological.

(*a*) Lesions of Other Endocrine Glands.—1. *Pituitary Glands.*—The pituitary gland in diabetes shows, so far as we are aware, no constant, significant change. Kraus[67] described adenomatous proliferation of acidophils, with areas of cellular degeneration and vacuolation of basophils in some cases. Cunz[68] claimed to find an increase in "chief cells" (immature non-granulated forms) indicating a "shift to the left" or maturation arrest. We have not been able to confirm these findings in our material. The variability of the cell population of the pituitary is, of course, well known.

with hyperfunction of the adrenal cortex in diabetes, will require confirmation.

As noted elsewhere in this book, the incidence of glycosuria in acromegaly is fairly high. However, if growth hormone is actually a major factor in the etiology of human diabetes, it is not clear why the incidence of diabetes is not even higher in acromegaly.

2. *Adrenal Glands.*—We have not found any constant change in the adrenal cortex or medulla. Apparent hyperplasia of the adrenal cortex

[58] Bondy and Cardillo. Jour. Clin. Invest. 35: 494, 1956.
[59] Caren and Carbo. Jour. Clin. Endocrinol. and Metab. 16: 507, 1956.
[60] Anderson, Monceo, Perfetto and Termine. Diabetes 6, 239, 1957.
[61] Gepts. Loc. cit. p. 177.
[62] Kenny. Jour. Clin. Endocrinol. and Metab. 15: 1089, 1955.
[62a] Beringer, Burkl and Steinhardt. Wien. klin. Wchnschr. 68: 101, 1956.
[63] Bencosme, Mariz and Frei. Loc. cit. p. 178.
[64] Salter, Davidson and Best. Diabetes 6: 248, 1957.
[65] Lacy. Ibid. 6: 498, 1957.
[66] Bencosme. Endocrinology 63: 1, 1958.
[66a] Moschcowitz. loc. cit. p. 173.
[67] Kraus. in Handbuch der spez. Path. u. Histol., ed. by F. Henke and O. Lubarsch, Berlin, J. Springer, vol. 8, 1926.
[68] Cunz. Schweiz. med. Wchnschr. 75: 561, 1945.
[69] Heskel. Jour. Albert Einstein Med. Center 5: 180, 1957.

In one of the most important monographs on diabetes to appear in recent years, Gepts[46] presents quantitative studies which in general support those of Maclean and Ogilvie. In a series of diabetic pancreases, he found an increase in the proportion of alpha cells but emphasized that this was due, not to a true hyperplasia of these cells but to a diminution in number of beta cells. The latter finding he considered to be "quasi constant" in diabetes. In a remarkably well balanced discussion, he points out that most of the "normal" pancreases found in diabetics in the past were so regarded *because of inadequate technique (i.e. lack of specific granule stains)* and that in the majority of cases of spontaneous diabetes a quantitative inferiority of the beta cells can be demonstrated.

The disc ... d interest in the alpha cells, ... sonable proof of the latter ... *Benscome and* co-workers,[49,50,51] who have ingeniously made use of the fact that part of the uncinate process of the dog's pancreas is normally devoid of alpha cells). Considerable confusion has arisen because of the fact that a hyperglycemic factor or factors can be extracted from the mammalian stomach and duode-

superficial, and there are fundamental histochemical differences.[51,52,53] The possibility that histochemical methods for tryptophan may serve to localize

means of an ... gents (cobalt, diethylthiocarbamate, certain of the sulfonylurea drugs and synthalin A) have proved generally fruitless, since the first three are relatively ineffective[54] and synthalin A damages the liver and perhaps affects the alpha cells as a consequence of this.[55] The general subject of alpha cell cytotoxins is well reviewed by Creutzfeldt.[56]

A further natural consequence of the demonstration that the alpha cells are probably the source of glucagon has been the hypothesis that a balance or antagonism may exist between glucagon and insulin, and hence between alpha and beta cells. This point of view has been upheld chiefly by Ferner,[57] *who has emphasized the ratio of the two cell types as of major importance.* However, increasing doubts have been expressed, not only as to the value of silver methods in estimating such a ratio, but also as to whether glucagon does in fact play a physiologic, homeostatic role in regulating the blood

[46] Gepts. Loc. cit., p. 177.
[47] Volk, *Lazarus and Goldner.* Arch. Int. Med., *93*, 87, 1954.
[48] Korp and LeCompte. Diabetes, *4*, 347, 1955.
[49] Bencosme, Liepa and Lazarus. Proc. Soc. Exper. Biol. and Med., *90*, 387, 1955.
[50] Bencosme and Mariz. Canad. Jour. Biochem. and Physiol., *34*, 779, 1956.
[51] Bencosme, Mariz and Frei. Lab. Invest., *7*, 138, 1958.
[52] Lodden. Am. Jour. Clin. Path., *23*, 991, 1953.
[53] Gomori. Jour. Histochem. and Cytochem., *2*, 50, 1954.
[54] Levine and Glenner. Jour. Nat. Cancer Inst., *20*, 63, 1958.
[55] Creutzfeldt and Tecklenborg. Arch. exper. *Path. u. Pharmakol.*, *227*, 23, 1955.
[56] Creutzfeldt. Diabetes, *6*, 135, 1957.
[57] Ferner. Loc. cit., p. 176.

In the *pancreas* glycogen may appear in both the islet cells (see above under *Hydropic Change*) and the duct epithelium The *kidney* shows the classical localization in Henle's loops, a finding which has been shown experimentally to be dependent on the height of the terminal blood sugar.[79, 80] In *voluntary muscle* there is a tendency to a decrease in glycogen In the *eye* there is

described as containing glycogen deposits

Insulin treatment causes the glycogen in the tissues to resume a more normal distribution The reasons for the rather bizarre location of the deposits in the untreated diabetic are quite obscure.

C MANIFESTATIONS OF DISTURBED FAT METABOLISM

Spleen and Reticulo-endothelial System —Lipoid histiocytosis, *i e*, hyperplasia of reticulo-endothelial cells with phagocytosis of lipids in the spleen and to a lesser extent in other organs as well, is a rare finding in cases which have had a marked lipemia

Skin —Xanthoma diabeticorum, or xanthoma eruptivum, is appar-

appear or disappear ac-

a nodular swelling, often

stologically, it is almost indistinguishable from xanthoma tuberosum, being made up of lipid-containing macrophages with occasional "Touton giant cells" (this is a cell with centrally arranged nuclei grouped around a small focus of non-foamy cytoplasm) The peripheral inflammatory reaction is said to be greater than that in xanthoma tuberosum The lesion is to be distinguished from xanthelasma or xanthoma palpebrarum, which is a small flat, yellowish plaque on the eyelid not particularly characteristic of diabetes

Necrobiosis lipoidica diabeticorum is not confined to diabetes, although about 90 per cent of cases occur in diabetics [81] The gross lesion is said to go through four stages (1) a small reddish infiltrated papule (2) an increasingly large lesion becoming violescent, (3) a slightly raised, firm yellow plaque which may soften and sometimes ulcerate, and (4) a flattened yellowish region with central atrophy and depression and a peripheral, irregular, scaling red or violescent region of infiltration Microscopically there is necrobiosis of collagen with homogenization and degeneration of fibers The lipids, the nature of which is obscure are characteristically extracellular

Gall Bladder. It is probable that the incidence of gall stones is slightly increased in diabetes Whether this should be attributed to the lipemia which the patients sometimes exhibit, or to their increased susceptibility to infection, or to some other cause is not settled

Liver An enlarged liver is a frequent clinical finding in diabetes and fatty infiltration has been a common pathological discovery in the

[79] Curtis, Robbins and Glickman Jour Exper Med 85 373 1947
[80] Robbins Am Jour Med Sci 219 376 1950
[81] Hildebrand, Montgomery and Rynearson Arch Int Med 66 851 1940

must be interpreted with care, since it *may be a non-specific response to stress*. In fact, some physiological evidence suggests that there may be a *lowered* adrenal cortical reserve in diabetes.[70, 71]

The occurrence of diabetes in association with the rare adrenal cortical tumors, and the occasional cure of the diabetes by the removal of such a tumor, is well known. Of even greater interest, perhaps, is the fact that cases of pheochromocytoma of the adrenal medulla have been reported, with cure or marked improvement of the diabetes following removal of the tumor.[72] The mechanism is presumably through stimulation of the "pituitary-adrenal axis" by epinephrine, with secondary overproduction of adrenal cortical steroids.

Hinerman's[73] contention that the islands of Langerhans are uniformly hyperplastic in cases of Addison's disease is not confirmed by Sloper.[74]

3. *Other Endocrine Glands*.—We have found no constant changes in other endocrine glands. However, Goddard and Sommers,[75] by a careful study of cell types in the thyroid, have found a significantly increased activity of colloid resorption and hence an inferred increased secretion of thyroid hormone.

(*b*) OBESITY.—The importance of obesity as a contributory etiological factor in diabetes needs no emphasis here.

(*c*) NEUROLOGICAL LESIONS.—These are mentioned only to be dismissed

been

is a

ave

not been confirmed, as far as we are aware.

B. MANIFESTATIONS OF DISTURBED CARBOHYDRATE METABOLISM

As will be noted later, it is possible to conceive of practically all the lesions characteristic of diabetes as representing disturbances in the metabolism of polysaccharides of ... most obvious and easily demonstrate ... o with the deposition of glycogen ... glycogen[76] (30 to 50 per cent above normal according to Cruickshank[77]), and this is often demonstrable especially around the margins of old infarcts. In the *liver* glycogen is often found within the liver cell nuclei and in less than *normal amounts in the cytoplasm, particularly in inadequately treated* cases. Recent experimental work[78] suggests that the glycogen may be a secondary deposit in a nucleus already vacuolated by osmotic disturbances

1, 77, 195, 1951

ed by S. Soskin, New York,

[77] Cruickshank

[78] Baird and Fisher. Lab. Invest., 6, 324, 1957.

past. Zimmerman *et al.*,[82] using needle biopsies of the liver, found fatty change of varying degree in 14 of 28 well-controlled diabetics, and in 3 of these cirrhosis was also found. These authors also found a positive correlation between the occurrence of fatty change and insensitivity to insulin, but they did not postulate a causal connection between the two.

D. THE SO-CALLED COMPLICATIONS OF DIABETES

Most of the "complications" of diabetes consist of diseases of the blood vessels and bacterial infections. Those vascular lesions which involve the capillaries and which are discussed below under "The Kidney" and "The Eye" are so characteristic of diabetes that they should perhaps be considered a part of the disease rather than as complications.[83,83a]

Atherosclerosis.—This type of arterial disease, characterized by the fatty plaque in the intima of the vessel, does not differ in kind from that found in non-diabetics. However, diabetics develop it at an earlier age and in more severe form than do non-diabetics. The incidence of coronary

twenties or thirties. Excellent papers on the subject are those of Bell[85] and of Liebow and Hellerstein.[86]

The frequency of gangrene of the lower extremities is too well known to require emphasis.[87] Strangely enough, sclerosis of the cerebral vessels is not an outstanding cause of death in diabetes.

The reason for the high incidence of atherosclerosis in diabetes is not at

tion of calcium in the media of arteries, particularly those of the extremities, is also more common in diabetics. Although the calcification, as seen in the *x*-ray film, has no significance as regards patency of the vessel under observation, it nonetheless has proved useful as a clinical index of vascular disease, especially in the younger patients.

Arteriolar Sclerosis.—*This lesion, again, does not differ in kind from* that found in non-diabetics. It is, however, more common in diabetics. Thus Bell[92] found arteriolosclerosis of the renal vessels over four times as frequent in diabetics over fifty years of age as in controls of comparable age. This increased incidence does not seem to be explainable by the only

[82] Zimmerman *et al.* Jour. Lab. Clin. Med., *36*, 912, 922, 1950.
[83] LeCompte. Jour. Chronic Dis., *2*, 178, 1955.
[83a] Ashton. Advances in Ophthalmology, *8*, 1, 1958.
[84] Warren and LeCompte. loc. cit., p. 170.
[85] Bell. Arch. Path., *53*, 444, 1952.

57
I, C C Thomas,
1956.
[92] Bell. Proc. Am. Diab. Assn., *10*, 62, 1950.

slightly higher incidence of hypertension in diabetics. He emphasizes the characteristic involvement of the efferent arteriole of the glomerulus.

The Kidney.—The principal lesions which may be found in the diabetic kidney are: (*a*) presumably reversible metabolic phenomena, such as deposits of glycogen or fat in the tubules, (*b*) arteriolar sclerosis involving both afferent and e

and (*d*) acute and c

litis. Any or all of

same kidney, and in fact the young diabetics of long duration characteristically show a mixture of lesions ("mixed diabetic nephropathy").[94] Indeed, it would seem that the common clinical diagnosis of "Kimmelstiel-Wilson disease" should be tempered with recognition of this fact.

Intercapillary glomerulosclerosis is very nearly, if not entirely, specific for diabetes.[95] It occurs in two forms, nodular and diffuse, which have been clearly distinguished by Bell.[93] The former is the most characteristic and easily recognized and consists of the presence of one or more ball-like hyaline masses in the glomerular tuft, having typically an intact capillary running over the surface of the nodule (see Plate I). The nature of the hyaline material is unknown; it seems to contain polysaccharides which are

and efferent arterioles.

[93] Bell ... 1953.

...ger, 1950.

...e and Strat-

Legend for Plate I

(From Warren and LeCompte: The Pathology of Diabetes Mellitus. Philadelphia, Lea & Febiger, 3d ed., 1952.)

A, Normal human island of Langerhans. Gomori's aldehyde-fuchsin counterstained with his trichrome method. β cells purple, α cells red, D cells pale green. Slide by courtesy of Dr. G. Gomori.

B, So-called "hydropic degeneration" in cells of island of Langerhans from human case of diabetes. The purple granules represent glycogen. Periodic acid-Schiff reagent method.

C, Island of Langerhans of normal rabbit. Gomori's chrome alum hematoxylin and phloxine stain.

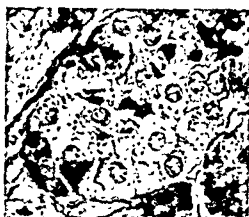
D, Island of Langerhans from rabbit made permanently diabetic with alloxan. It consists entirely of α cells with the possible exception of three or four "hydropic" β cells.

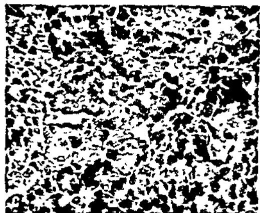
E, Glomerulus from kidney showing intercapillary glomerulosclerosis. The "axial" distribution of the lesion, tendency to nodular aggregation with intact capillaries on the surface, and hyalinization of both afferent and efferent arterioles are shown. Periodic acid-Schiff reagent method.

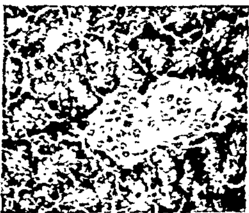
F, Whole mount of diabetic retina showing a large arteriole, several capillaries and a capillary microaneurysm. Friedenwald's modification of Hotchkiss' method.

PLATE I

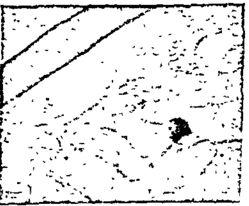












infarct-like necrosis occurs at the tips of the pyramids in the medulla, sometimes with sequestration of the end of the pyramid into the pelvis, with resulting hematuria and renal colic. The pathogenesis is obscure; small hyaline thrombi may be found in the medullary vessels in addition to various kinds of bacteria (usually staphylococci and members of the coliform group).

The Eye.—Most of the ocular changes in diabetes are well summarized in the classical paper of Waite and Beetham.[114] The deposition of glycogen in the pigmented epithelium of the iris has been mentioned above. Recent advances have been concerned chiefly with the retinopathy. Some emphasis has been placed on the frequency of venous varices and of phlebosclerosis. Greatest interest, however, has centered on the *capillary microaneurysms* described by Ballantyne[115] and studied especially by Friedenwald[116] and Ashton.[117] These small sac-like dilatations of the capillaries, sometimes filled with blood, sometimes with laminated hyaline material, probably represent in large part the so-called punctate retinal hemorrhages long regarded as characteristic of diabetic retinopathy. Their essential aneurysmal nature has been demonstrated beyond doubt by Friedenwald's adaptation of Hotchkiss' periodic acid-Schiff reagent method to whole mounts of retina (see Plate I).

Although retinal micro-aneurysms and intercapillary glomerulosclerosis are frequently coexistent, it does not necessarily follow that the glomerular lesions are fundamentally aneurysmal also.[118] The reason for the high susceptibility of the capillaries of the eye and kidney is obscure, but may be related to the fact that the capillary pressure is higher in these two places than anywhere else in the body.[119]

Another fairly common and most distressing lesion is *retinitis proliferans*, (see Chapter 22) in which a delicate highly vascularized connective tissue extends out from the optic disc into the vitreous. The condition seems to be associated with the organization of the repeated retinal hemorrhages so common in these patients, and perhaps may be regarded, from the standpoint of the general pathologist, as equivalent to an organizing hematoma in other tissues.

Another change seen occasionally in the diabetic eye is occlusion of the central retinal vein, either by thrombosis or intimal proliferation, with consequent formation of a peculiar connective tissue membrane on the anterior surface of the iris.

It is still uncertain whether *cataract* is more prevalent in diabetics than in the general population, and whether the cataracts that can be produced so easily in alloxan diabetic rats differ pathologically[120] or chemically[121] from other types. The experimental ones are said to be prevented,[122] or when once established, ameliorated by[123] insulin.

[114] Waite and Beetham: New England Jour. Med., 212: 429, 367, 1935.
[115] Ballantyne: Arch. Ophth., N.S. 33: 97, 1945.
[116] Friedenwald: Am. Jour. Ophth., 33: 1187, 1950.
[117] Ashton: Brit. Jour. Ophth., 33: 407, 1949.
[118] Kimmelstiel: Jour. Mt. Sinai Hosp., 23: 657, 1956.
[119] LeCompte: loc. cit., p. 182.
[120] Friedenwald and Rytel: Arch. Ophth., 53: 825, 1955.
[121] Waters: Biochem. Jour., 46: 575, 1950.
[122] Rodriguez and Krehl: Yale Jour. Biol. and Med., 24: 103, 1951-52.
[123] Cohen and Kok van Alphen: Acta physiol. et pharmacol. neerl., 3: 81, 1953.

Estimates of the incidence of the lesion vary widely, due mainly to differences in interpretation of the nodular and diffuse lesions. Our own estimate of the frequency is about the same as that of Kimmelstiel and Porter[100] (17 per cent). The incidence is very high in the young diabetics of long duration, in which group renal insufficiency is emerging as a major cause of death. The clinical recognition of intercapillary glomerulosclerosis is discussed elsewhere.

The last few years have witnessed an increasing number of papers on another type of change, termed the "exudative" lesion by some, which exists in the presence of hyaline glassy, homogeneous or vacuolated deposits within the lumen of the glomerular capillaries or within the capsular space ("capsular drop"). This material contains fat, glycoprotein, hemoglobin and sometimes intact red cells It was described by Kimmelstiel and Wilson[101] in their original paper, and was properly not emphasized by them It is not specific for diabetes, and in fact seems to be a late phenomenon, occurring with renal failure, and hence is probably not of pathogenetic significance.[102]

The importance of this "exudative lesion" lies in the fact that it is being confused in current literature with the classical nodular lesion which was originally delineated by Kimmelstiel and Wilson and which has been shown to be probably quite specific for diabetes. Thus the statement is made[103] that "the Kimmelstiel-Wilson lesion is not absolutely specific for diabetes" without clear
is being discu-
trations of st
in which hyaline material is shown lying within a capillary loop and apparently within endothelial cells, may represent the exudative lesion

Equally unfortunate, perhaps, is the fact that something like the exudative lesion (i e intracapillary hyaline masses) can be produced in animals with cortisone[105] or prednisolone,[106] and that such lesions are reported as "resembling" the nodular lesion of intercapillary glomerulosclerosis, with the implication that the adrenal cortex may play an important role in the production of renal disease in diabetes,[107] whereas actually the evidence for

F

four

Weiss and Parker[113] Recently increasing attention has been devoted to a particular type of acute pyelonephritis, *necrotizing renal papillitis*, in which

[100] Kimmelstiel and Porter New Engl and Jour Med, 238, 876 908, 1948
[101] Kimmelstiel and Wilson Am Jour Path, *12*, 83, 1936
[102] LeCompte loc cit p 182
7, 1958
293, 1957
1956
h, *65*, 340, 1958
, 9, 1958
951
9

infarct-like necrosis occurs at the tips of the pyramids in the medulla, sometimes with sequestration of the end of the pyramid into the pelvis, with resulting hematuria and renal colic. The pathogenesis is obscure, small hyaline thrombi may be found in the medullary vessels in addition to various kinds of bacteria (usually staphylococci and members of the coliform group).

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[114] Waite and Beetham: New England Jour. Med., *212*: 219, 367, 1935.
[115] Ballantyne: Arch. Ophth., NS 33: 97, 1945.
[116] Friedenwald: Am. Jour. Ophth., 33: 1187, 1950.
[117] Ashton: Brit. Jour. Ophth., 33: 407, 1949.
[118] Kimmelstiel: Jour. Mt. Sinai Hosp., *23*: 657, 1956.
[119] LeCompte: loc. cit., p. 182.
[120] Friedenwald and Rytel: Arch. Ophth., *53*: 825, 1955.
[121] Waters: Biochem. Jour., *47*: 575, 1950.
[122] Rodriguez and Krehl: Yale Jour. Biol. and Med., *24*: 103, 1951-52.
[123] Cohen and Kok van Alphen: Acta physiol. et pharmacol. neerl., 3: 81, 1953.

Other Vessels.—The *in vivo* studies of Ditzel[124] on conjunctival ves-

describes are apparently non-specific.

Diabetic Neuropathy.—This condition has no characteristic histological picture. In fact, due to the transitory nature of the process, nerves are rarely available for study. Attempts to explain it on the basis of arteriolar sclerosis[127,128] or vitamin deficiency are not convincing. Neuropathic lesions of the foot, analogous perhaps to the Charcot joint, have been described.

Complications or Concomitants?—The vascular lesions of diabetes are usually regarded as complications, the assumption being that they somehow result from metabolic alterations of the disease (see below). It is possible, however, that the vascular alterations might be concomitants, *i.e.* genetically determined along with the diabetes but not a consequence of the metabolic disturbance.[128a] In this connection the extreme rarity of

of such cases

E. IS THERE A COMMON DENOMINATOR?

Perhaps the most striking characteristic of the lesions that may be found [illegible] e and un- [illegible] However, [illegible] ht justify [illegible] pointing out the frequency with which retinal microaneurysms and intercapillary glomerulosclerosis occur in the same individual, also the similarity in staining reactions of the two lesions, and cited the work of Jacobs[130] on serum mucopolysaccharides in diabetes and of Pirani[131] on amyloidosis in experimental scurvy as possibly indicating a common basis for the retinal and renal alterations.

We[132] have attempted to extend this suggestion of Friedenwald's to *embrace most of the other lesions found in diabetes.* Some justification for this point of view may be found in work[133,134] which emphasizes the impor-

[illegible] *44*, 386, 1956

[illegible] d., *51*, 370, 1958
[illegible] ed., *35*, 1028, 1951
[illegible] 957

[illegible] et, *1*, 822, 1958

[illegible] 1949

[illegible] *Sci.*, *52*, 943–1196, 1950
[illegible] *85*, 457, 1949

tance of mucopolysaccharides as constituents of "ground substance," basement membrane of capillaries, and the like. These substances must be involved in the unknown physico-chemical changes which result in the

category of a deposit of complex polysaccharide-proteins[135] Altshuler and Angevine[136] have pointed out the probable importance of the acid mucopolysaccharides in "degenerative" processes or deposits in connective tissue such as "hyalin," "amyloid," "sclerosis," and "fibrinoid degeneration," many of which of course occur in diabetes Thus it is possible to conceive of most of

orders in th

or (b) com

tempts to correlate levels of serum polysaccharides with vascular "complications" of diabetes[137] [138] have been fraught with difficulty, since it is usually impossible to be sure that elevated polysaccharide levels may not be the consequence rather than the cause of the vascular disease The situation is especially confused since directly opposite changes have been found in experimental diabetes in rats[139]

F CAUSES OF DEATH IN DIABETES

A tabulation of the causes of death in diabetes is given in Table 31 Further data are given by Warren and LeCompte,[140] and in the papers by Robbins and Tucker,[141] and by Bell[142] The recession of coma as a leading cause of death is, of course, well known, and in recent years, due largely to the antibiotics, infection has become less important One of the most striking developments in recent years is the predominance of coronary disease as a terminal episode in the middle-aged and older diabetics, and of renal disease in the young diabetics of long duration

G POST-MORTEM DIAGNOSIS OF DIABETES

In making a diagnosis of diabetes at the autopsy table, chemical methods are, of course, valuable and should be tried Blood for glucose determination should be taken from the *left* heart (to avoid diffusion of glucose from the liver) A value of over 200 mg per cent may be significant although

[135] Rinehart Toreson and Abul-Haj Am Jour Med 17 124 1954
[136] Altshuler and Angevine Am Jour Path [illegible] 141 1951
[137] Berkman Diabetes 4 265 1955
[138] Keiding Protein-bound carbohydrates and proteins of serum from diabetic patients, Copenhagen Steno Mem I Hosp 1957
[139] Nichols Monat and Fuller Diabetes 5 468 1956
[140] Warren and LeCompte loc cit p 170
[141] Robbins and Tucker New England Jour Med 231 865 1944
[142] Bell loc cit, p 182

TABLE 31 — THE CAUSES OF

Cause of Death	Naunyn Era 1898 to 5/31/14 Deaths	Per Cent of all Cases	Allen Era 6/1/14 to 8/6/22 Deaths	Per Cent of all Cases	Banting Era 8/7/22 to 12/31/36 Deaths	Per Cent of all Cases
All Causes	326	100.0	836	100.0	4,138	100.0
A Coma present	208	*63.8*	*347*	*41.5*	343	*8.3*
B Coma absent						
1 Cardio-renal-vascular	57	17.5	206	24.6	2,251	54.4
Arteriosclerotic	57	17.5	203	24.3	2,235	54.0
a Cardiac	20	6.1	83	9.9	1,234	29.8
b Nephritic	11	3.4	32	3.8	199	4.8
c Apoplexy	9	2.8	41	4.9	386	9.3
d Gangrene	*12*	*3.7*	*35*	*4.2*	*329*	*8.0*
e Site unassigned	5	1.5	12	1.4	87	2.1
Other, including rheumatic ht. dis.	0	0.0	3	0.4	16	0.4
2 Infections, total	24	7.4	106	12.7	563	13.6
Pneumonia and resp.	14	4.3	64	7.7	283	6.8
Throat and ear	0	0.0	6	0.7	22	0.5
Gall Bladder	*0*	*0.0*	*4*	*0.5*	*20*	*0.5*
Appendicitis	2	0.6	3	0.4	25	0.6
Carbuncle	6	1.8	13	1.6	40	1.0
Kidney, acute	0	0.0	1	0.1	37	0.9
Abscesses	0	0.0	7	0.8	59	1.4
Other Infections	2	0.6	8	0.9	77	1.9
3 Cancer	5	1.5	32	3.8	362	8.7
4 Tuberculosis	*16*	*4.9*	*41*	*4.9*	*170*	*4.1*
5 Diabetes (unknown)	8	2.5	56	6.7	124	3.0
6 Accidents	0	0.0	7	0.8	85	2.1
7 Inanition	1	0.3	18	2.2	6	0.1
8 Suicides	1	0.3	2	0.2	28	0.7
9 Insulin reactions	0	0.0	0	0.0	8	0.2
10 Other diseases	6	1.8	21	2.5	198	4.8

*Deaths reported through December 11, 1957 Each death, 1897–1957, certified by E P J Checked
Note Figures for 1950 and later are not strictly comparable with those for earlier periods because of changes in the basis of classification

Hill[143] and Fisher[144] caution that agonal release of epinephrine from the adrenal glands may lead to high glucose levels even in non-diabetics The use of cerebrospinal fluid, obtained by cisternal puncture, as recommended by Naumann,[145] would not be expected ...erhaps significant, as is ...ed for sugar and acetone

The presence of glycogen in the islands of Langerhans is considered by Toreson[146] to be positive morphological proof of the existence of diabetes mellitus Glycogen in the renal tubules is also fairly conclusive, and helpful, though not specific, evidence is provided by depletion of glycogen *in the cytoplasm of the liver cells and its presence in the nuclei* The finding of advanced hyalinization of the islands, of typical intercapillary glomeru-

[143] Hill Arch Path, *32*, 452, 1941
[144] Fisher New England Jour Med, *243*, 976, 1950
[145] Naumann Arch Path, *47*, 70, 1949
[146] Toreson loc cit, p 175

...DEATH OF 18,055 DIABETICS*

Hagedorn Era				*Charles H Best Era*			
1/1/37 to 12/31/43		1/1/44 to 12/31/49		1/1/50 to 12/31/55		1/1/56 to 12/31/57	
Deaths	*Per Cent of all Cases*	*Deaths*	*Per Cent of all Cases*	*Deaths*	*Per Cent of all Cases*	*Deaths*	*Per Cent of all Cases*
,023	100.0	4,116	100.0	4,376	100.0	640	100.0
102	2.8	71	1.7	55	1.3	7	1.1
2,383	65.8	2,935	71.3	3,340	76.3	497	77.7
2,366	65.3	2,908	70.7	3,310	75.6	495	77.3
,490	41.1	1,939	47.1	2,153	49.2	321	50.2
166	4.6	239	5.8	433	9.9	72	11.3
428	11.8	527	12.8	565	12.9	80	12.5
192	5.3	119	2.9	81	1.9	15	2.3
90	2.5	84	2.0	78	1.8	7	1.1
17	0.5	27	0.7	30	0.7	2	0.3
375	10.4	243	5.9	235	5.4	25	3.9
200	5.5	150	3.6	138	3.2	8	1.3
3	0.1	0	0.0	0	0.0	0	0.0
21	0.6	13	0.3	15	0.3	3	0.5
19	0.5	6	0.1	7	0.2	1	0.2
18	0.5	1	0.0	1	0.0	0	0.0
32	0.9	26	0.6	24	0.5	2	0.3
29	0.8	9	0.2	7	0.2	2	0.3
54	1.5	38	0.9	43	1.0	9	1.4
326	9.0	400	9.7	452	10.3	72	11.3
79	2.2	69	1.7	32	0.7	1	0.2
126	3.5	107	2.6	30	0.7	1	0.2
67	1.8	86	2.1	87	2.0	11	1.7
0	0.0	0	0.0	2	0.0	0	0.0
23	0.6	24	0.6	21	0.5	3	0.5
10	0.3	10	0.2	9	0.2	1	0.2
132	3.6	171	4.2	113	2.6	22	3.4

...and compiled by the Statistical Bureau, Metropolitan Life Insurance Company

losclerosis, of hyalinization of the efferent as well as the afferent arteriole of the glomerulus, or of numerous capillary microaneurysms in the retina, is almost pathognomonic As regards differential cell counts on the islands, it is probably safe to say that a ratio of beta to alpha cells of less than 3 is strongly suggestive of diabetes The development of newer staining methods has made such counts more practical than heretofore Also, the presence of extensive degranulation of the beta cells is strongly suggestive of diabetes.[147]

There are thus several findings, any one of which is highly suggestive If two or more are found in the same autopsy the diagnosis becomes more conclusive

II INFANTS OF DIABETIC MOTHERS

It has been recognized for years that there is a distressingly high fetal and neonatal mortality among the offspring of diabetic mothers The large

[147] Bell Am Jour Clin Path 25, 299 1955

Table 31.—The Causes of

Cause of Death	Naunyn Era 1898 to 5/31/14 Deaths	Per Cent of all Cases	Allen Era 6/1/14 to 8/6/22 Deaths	Per Cent of all Cases	Banting Era 8/7/22 to 12/31/36 Deaths	Per Cent of all Cases
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Carbuncle	6	1.8	13	1.6	40	1.0
Kidney, acute	0	0.0	1	0.1	37	0.9
Abscesses	0	0.0	7	0.8	59	1.4
Other Infections	2	0.6	8	0.9	77	1.9
3 Cancer	5	1.5	32	3.8	362	8.7
4 Tuberculosis	16	4.9	41	4.9	170	4.1
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Hill[143] and Fisher[144] caution that agonal release of epinephrine from the adrenal glands may lead to high glucose levels even in non-diabetics The use of cerebrospinal fluid, obtained by cisternal puncture, as recommended by Naumann,[145] seems logical, since sudden changes in glucose level would not be expected Here again, a level of over 200 mg per cent is perhaps significant, as is the presence of acetone The urine may be tested for sugar and acetone

The presence of glycogen in the islands of Langerhans is considered by Toreson[146] to be positive morphological proof of the existence of diabetes mellitus Glycogen in the renal tubules is also fairly conclusive, and [illegible]

[143] Hill Arch Path, 32, 452, 1941
[144] Fisher New England Jour Med, 243, 976, 1950
[145] Naumann Arch Path, 47, 70, 1949
[146] Toreson loc cit, p 175

mother during pregnancy

[113] Hultquist and Engfeldt. Acta Endocrinol., 3, 365, 1949

size of the infants, not only of diabetic women, but also of many women who later develop diabetes, is also well known. In several respects too, these babies have been shown to resemble those suffering from erythroblastosis fetalis, so much so that the two conditions may be confused at necropsy.

A series of 50 infants, from the service of Drs. Priscilla White and R. S. Titus, autopsied at the Faulkner Hospital, has recently been reviewed in detail.[148] In most cases the cause of death was obscure, although hyaline membrane disease was common.[149] The incidence of congenital anomaly was high (18 per cent of the cases, fatal in 6 per cent). Certain findings were

and treated, as large prematures rather than as "postmature" infants.

2 *Visceromegaly* —Enlargement of the heart occurred frequently enough to be considered significant In the past this has been considered to be due, at least in part, to glycogen, but the investigations of Curtis seem to negate this hypothesis.[150] Definite enlargement of the liver and spleen was found in only a few cases, and was not considered to be clearly significant.

3 *Pancreas* —Two changes were found often enough to be considered significant: (*a*) hyperplasia of the islets of Langerhans, and (*b*) infiltration of the islets by eosinophil leukocytes [151] The causes of these phenomena are not known.

4 *Hematopoiesis*.- It was not clear that extramedullary blood formation was increased out of proportion to the prematurity of the infants

5 "*Glycogen nephrosis*" – Glycogen was observed in the renal tubules of some of the infants However, its specificity may be questioned [152]

6 *Gonads* Follicle development was prominent in the ovaries of several female infants, and a decidual reaction was seen in the endometrium of one. Others[153 154] have found ovarian cysts in these infants

7 *Placenta* Many of the placentas were heavier than a control series This may be another indication of prematurity We have not found any distinctive histological changes Burstein *et al* [155] describe an endarteritis of the placental vessels characterized by reduplication of the basement membrane, endothelial proliferation and deposits of mucopolysaccharide

Many of these findings have been confirmed by Cardell [156] Their cause remains a matter for speculation [157]

The experimental reproduction of these changes has been difficult Hultquist[158] using partial pancreatectomy in rats, was able to obtain a few

[148] Warren and LeCompte *Loc cit* p 170
[149] Winter and Gellis Diabetes, *3*, 410, 1954
[150] Curtis Work in progress
[151] McKay, Benirschke and Curtis Obst and Gynec, *2*, 133, 1953
[152] Hinde Jour Path and Bact, *61*, 451, 1949
[153] Ober and Bernstein Pediatrics, *16*, 445, 1955
[154] Ahlvin and Bauer Am Jour Dis Child, *93*, 107, 1957
[155] Burstein, Soule and Blumenthal Am Jour Obst and Gynec, *74*, 96, 1957
[156] Cardell Jour Obst and Gynec Brit Empire, *60*, 834, 1953
[157] Hoet Diabetes, *3*, 1, 1954
[158] Hultquist Acta path et microbiol Scand, *25*, 131, 1948, *27*, 695, 1950

The Volume of Urine in Twenty-four Hours.—The average normal quantity of urine is 1200 to 1800 cc. (40 to 60 ounces) a day In diabetic patients the amount

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twenty-four hours may give but little index of the severity of diabetes The twenty-four hour quantity of urine may be normal and yet contain a significant amount of sugar

The volume of urine should be expressed in cubic centimeters since this enables the amount of sugar in the twenty-four-hour quantity of urine to be most readily calculated Volumes recorded in the English system by patients at home may, with sufficient accuracy for ordinary clinical work, be transposed by considering one fluid ounce 30 cc and one quart 1000 cc

In hospital or summer camps, to facilitate measurement of the volume of the urine, wide-mouthed, stoppered bottles, of 2000 cc. capacity graduated at intervals of 50 cc, may be employed If at all possible, the container for collection of the twenty-four-hour amount should be kept in the cold, if left at room temperature, the addition of a few cubic centimeters of xylene or toluene as a preservative is desirable

The Specific Gravity —The normal average specific gravity of the urine is about 1 015 to 1.025 The specific gravity of the urine in uncontrolled diabetes is usually high, and in Case 18477 a value of 1 054 was found in a specimen containing 14 per cent sugar On the other hand, small amounts of sugar may be present in urine with a specific gravity of less than 1 010 A normal or low specific gravity is no more excuse for neglecting to examine the urine than is a normal quantity of urine

Sugars of Normal Urine.—It has long been known that the urine of presumably normal individuals gives the usual copper reduction tests characteristic of sugar if sufficiently sensitive reagents are used, the amount of these substances is found to vary between 0 01 and 0 1 per cent The nature of these reducing substances (non-nitrogenous) was a subject of controversy for years [3, 4, 5] Clarification of the matter has been aided greatly in recent years by the availability of relatively simple methods for the determination of amounts of glucose by means of the enzyme glucose oxidase The results of Froesch, Renold and McWilliams[6] in 30 normal persons are shown in Table 32 It is evident that in their subjects true glucose made up only about one-seventh of the total reducing substances Froesch *et al* found that glucose excretion was relatively independent of the amount of carbohydrate in the diet However, after the administration of hydrocortisone and other carbohydrate active adrenal steroids, there were significant increases

Glucose in Urine. (Dextrose, $C_6H_{12}O_6$) An adequate evaluation of the degree of control of diabetes is difficult to obtain unless the total quantity of sugar excreted in twenty-four hours is known For many years

[3] Benedict, Osterberg and Neuwirth Jour Biol Chem, *34*, 217, 1918, *55*, 769, 1923
[4] Folin and Berglund Ibid, *51* 213, 1922
[5] Peters and Van Slyke Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 2nd ed, vol *1*, Interpretations, p 189, 1946
[6] Froesch, Renold and McWilliams Diabetes, 5 1, 1956

Chapter 7

THE EXAMINATION OF THE URINE AND THE BLOOD IN DIABETES

ALEXANDER MARBLE, M.D.

A. THE EXAMINATION OF THE URINE

The Importance of Routine Examinations of Urine. The [illegible] of [illegible]

[illegible] by the American Diabetes Association, has demonstrated forcefully the [illegible]

analysis should form a part of every physical survey It is especially desirable to secure a specimen of urine within two hours after a hearty meal since it is not uncommon for this sample to contain sugar, while one obtained fasting or three or more hours after eating may be sugar-free

Neglect in examining the urine of any case coming for treatment may bring embarrassing or even disastrous results. The physician who was called to see Case 12139 failed to examine the urine, failed to recognize the condition of on-coming acidosis, and the patient died in diabetic coma thirty-six hours later, four hours after he was brought to the hospital in a moribund state The physician of Case 18373, seen for the first time in *diabetic coma, had told the patient one week previously that the abnormal* thirst was due to hard work

Examination of the urine for sugar should cost the patient little. Labora*tory service should be available even in small communities so that routine* urine and blood tests can be performed near the homes of patients. A laboratory may be life-saving, because with its help a patient in diabetic coma may receive insulin more promptly and a patient in hypoglycemia may be spared a death-dealing dose of insulin It is imperative that a hospital laboratory furnish service in emergencies at any hour, nights, Sundays and holidays A competent technician, not a poorly trained substitute, should be constantly on call to do thoroughly reliable work at times of real need

[1] Report of Committee on Diabetes Detection Proc Am Diabetes Assn, *10*, 262, 1950

[2] Blotner and Marble New England Jour Med, *245*, 567, 1951

As used with urine the test is sufficiently delicate to detect quantities as small as 0 08 or 0 1 per cent sugar, in which case a faint pea-green change in color takes place This green color changes to a yellowish-green when the urine contains about 0 5 per cent sugar When the solution loses the greenish tint entirely and becomes yellow or brown, the urine contains over 1 per cent sugar Above this percentage the color of the solution gives very little aid in estimating the amount of sugar in the urine, although large amounts of sugar will produce an orange, brown or red test.

Rarely urine specimens are encountered which, when tested, give a fluorescent appearance, due to a very fine, brick-red precipitation of the

in the urine On titration it is often found that there may be as much as 1 per cent sugar in a urine which tested qualitatively might be estimated as 0 2 per cent

It should be remembered that certain other sugars as lactose, galactose, pentose and levulose reduce Benedict's solution Their presence must be suspected in cases of normoglycemic melituria For methods of differentiation, see pages 198 and 199

2 *Rapid Methods*— In recent years various procedures have been devised to permit the quick and easy testing of the urine for sugar These include

(*a*) Clinitest[27] method, a modification of the Benedict test, in which a reagent tablet is dropped into a measured amount of diluted urine. Heat is generated within the test-tube by the contact of the tablet with the liquid, causing boiling which lasts a few seconds The colors produced by varying amounts of sugar are roughly those of the standard Benedict test and interpretations are made accordingly A color scale allows for the estimation of approximate percentages of sugar Since the tablets attract moisture and, having done so lose their potency, it is important they be kept in tightly stoppered or capped containers or purchased in a sealed, foil package

(*b*) Galatest[28] in which a white alkaline powder containing bismuth is used A drop or two of urine is placed on a small mound of the powder, the presence of sugar in the urine is indicated by the production of a gray or

[27] Made by the Ames Company, Inc , Elkhart, Indiana

[28] Galatest powder is made by the Denver Chemical Manufacturing Company, 163 Varick St , New York, N Y

with patients in the hospital and with children in summer camps, the authors have insisted that such information be obtained daily as an invaluable guide in treatment. The total volume is recorded, the percentage of sugar determined by rapid, convenient methods and the number of grams excreted is calculated. Wider adoption of this policy is urged since the work involved is minimal and the information gained is extremely helpful.

In teaching patients and others it is always impressive to illustrate the total amount of sugar excreted by a markedly glycosuric patient in twenty-four hours by exhibiting an equivalent amount of cane sugar. The total quantity, not the percentage, leaves the desired indelible impression of wastage of sugar.

TABLE 32.—TWENTY-FOUR-HOUR URINARY GLUCOSE EXCRETION IN 30 NORMAL SUBJECTS

(From Froesch, Renold and McWilliams[4])

	"Glucose" as measured by conventional methods (mg)	Glucose as measured by glucose oxidase method (mg)	Nonglucose reducing substances (mg)
Mean	511	72	439
Range	212-845	16-132	218-809

In many chronic diseases there is no criterion by which the success or failure of treatment can be readily estimated. Fortunately, in diabetes, one can tell when treatment is successful, for the patient should be free from sugar and diacetic acid and be happy and vigorous. Although the twenty-four-hour quantity of sugar in the urine is not an absolute measure of the degree of control of diabetes, in the majority of cases it is an accurate index.

The sugar in the urine of diabetic patients usually varies directly with the quantity of carbohydrate-forming material in the diet, to a lesser extent with the protein, still less with fat, except as that influences intake. A change of diet is shown in the urine within a few hours and sugar may appear within a few minutes after food.

QUALITATIVE TESTS.—Nearly all of the qualitative tests for glucose have the advantage that although mere traces of sugar may be present in the urine of normal individuals, they fail to demonstrate its presence unless the sugar exists in an amount greater than normal.

1. *Benedict's test* is the one most generally useful. This requires only a single solution which keeps indefinitely, and is not reduced by creatinine or uric acid.

[illegible]

urinary salts

For *rapid* reduction of the reagent vigorous boiling is essential, which may result

boiling solution becomes quite simple

3 *Sheftel's Method*—Sheftel[14] devised a method in which the colors produced by the reduction of a copper reagent are compared with those of a semi-permanent color chart It is simple to carry out and may be used by the patient in the home

4. *Di-nitro-salicylate Method*—This method, a modification of that used by Sumner[15] and Exton,[16] combines speed with accuracy and is useful

examined for

rodersen and

the last few

years in our office laboratory By carrying out the procedure with all urine specimens, it serves both as a qualitative and a quantitative test The preparation of the reagent and the method of determination are described below

Dissolve 1600 gm Rochelle salts in 2400 cc of warm distilled water Add 52 gm of phenol crystals Make up to 4000 cc with water Dissolve 48 gm of mono-sodium-3-5-dinitro-salicylate in 2800 cc of water which has been heated to 65° C

reagent in a test tube Place in boiling water for 3 min Allow to cool and read in a photoelectric colorimeter using a 660 mu filter

[14] Sheftel Med Jour and Rec, *126*, 663, 1927 See also Rhodehamel, Rose and Chen Med Rec, *145*, 321 1937 Apparatus and reagents may be purchased from

Mc

Proc 28th Annual

black color (reduction of the bismuth). The reaction is complete in less than thirty seconds.

(c) Adaptations of the glucose oxidase test. Two types are available: Tes-tape[9] and Clinistik[10]. Using Tes-tape, one dips a strip of yellow impregnated paper in the urine and notes the color change, if any, in one minute. The presence of glucose is indicated by varying shades of green and blue. Using Clinistik, one dips into the urine the specially treated tip of a paper stick. Color changes and the interpretation are similar to those with Tes-tape. *These methods have the advantage of being specific for glucose* and of possessing great speed and simplicity. They are particularly useful for the patient whose urine is always, or almost always, sugar-free and with whom testing serves to assure that absence of glycosuria continues.

QUANTITATIVE TESTS.—The more accurate of the quantitative procedures require a laboratory, but methods sufficiently correct for clinical work can easily be performed by the general practitioner, the nurse, or by more intelligent patients in the home. In fact, a reasonable approximation of the percentage of sugar in the urine may be obtained with the Clinitest apparatus described above and the Sheftel method mentioned later.

... casionally ... for treat- ... 5 and con- ... s reported ... ase 18477, December 6, 1939, the first specimen of urine had a specific gravity of 1.054 and contained 14 per cent sugar. A second specimen had a specific gravity of 1.053 and contained 13.2 per cent sugar. This patient died on June 27, 1955, in uremia, in life the situation had been that of the Kimmelstiel-Wilson syndrome and autopsy disclosed intercapillary glomerulosclerosis.

The quantitative tests listed below are described in original articles and in standard books on laboratory procedures, accordingly, for the most part they are given only brief mention here.

1. *Original Method of Benedict.*[11]—This original method, from which the various modifications have been devised, is too time-consuming for routine use. The procedure is based on the fact that in alkaline solution a given quantity of glucose reduces a definite amount of copper, precipitating it as cuprous sulphocyanate, which, being snow-white, is an aid to accurate observation of the disappearance of the last trace of color.

2. *The Micro-modification of Benedict's Test.*—This method, devised by Millard

... ma
... ndiana

[11] This may be purchased from many surgical supply houses or from the manufacturers, Emil Greiner Company, 55 Vandam St., New York City.

(c) FRUCTOSE (LEVULOSE), $C_6H_{12}O_6$.—Fructose occurs in the urine of individuals with essential fructosuria and is said to be present at times in the urine of patients with severe diabetes. It is levorotatory but so is β-oxybutyric acid, which is found under similar conditions. Fructose is fermented by yeast, like pentose, gives a positive Fehling and Benedict test after several hours even without heating or within ten minutes at 50° to 60° C.; and yields the same osazone as does dextrose with phenylhydrazine. With methyl-phenylhydrazine it gives a characteristic osazone, however. Fructose can be differentiated by the Seliwanoff reaction, provided the test is carefully performed and certain precautions followed. This test is carried out as follows:

is entirely soluble in alcohol

We have recognized only 4 instances of essential fructosuria. (See page 736.)

(d) MALTOSE ($C_{12}H_{22}O_{11}$).—Maltose rarely occurs in human urine, and has not been shown to be of clinical significance.

(e) SUCROSE ($C_{12}H_{22}O_{11}$).—The finding of sucrose, or cane sugar, in the urine has been reported only rarely except, of course, following the injection of this sugar intravenously, in which case it is promptly excreted, since

gravity of the urine leads one to think of the possibility of sucrose in the urine.

There is room for reasonable doubt as to whether there is such a condition as spontaneous sucrosuria. If it does exist, it has little or no clinical significance. However, Moncrieff and Wilkinson[21] considered sucrosuria to be the cause of marasmus in 3 mentally defective infants with hiatus hernias. Some years ago Elmer[22] reported 2 cases of sucrosuria and cited the relevant literature. In his patients the specific gravity of the urine reached values as high as 1.070.

appeared in the urine in amounts from 0.06 to 0.32 per cent.[23]

(g) SUBSTANCES FOUND IN THE URINE WHICH GIVE RISE TO CONFUSION IN TESTING FOR SUGAR.—Very few substances interfere with the accuracy

[18] Covey: Am. Jour. Clin. Path., *19*, 500, 1949.
[19] Lasker and Enklewitz: Jour. Biol. Chem., *101*, 289, 1933.
[20] Exton: Loc. cit., p. 197.
[21] Moncrieff and Wilkinson: Acta Pediat., 43, Supp. 100, p. 495, 1954. (Cited in Editorial, Brit. Med. Jour., *1*, 900, 1955.)
[22] Elmer: Pol. Arch. Med. Wewn., *16*, 449, 1938; Pol. Gaz. Lek., *17*, 491, 1938.
[23] Blatherwick, Larson and Sawyer: Jour. Biol. Chem., *133*, 643, 1940.

5 *Polariscopy and Fermentation*.—One may determine the amount of sugar by polariscopy or by fermentation with yeast, but these methods are by no means [illegible] es and are [illegible] fermenta- [illegible] presence of sugar is indicated, after a suitable incubation period, by the bulging of a rubber diaphragm covering the mouth of a tiny bottle containing a bit of yeast and filled with urine.

Tests for Other Sugars.—Sugars other than glucose are found in urine sufficiently often to make it imperative that one ascertain the type of sugar [illegible] As has been stated earlier, differentiation from glucose is aided by the newly introduced glucose oxidase methods and by paper chromatography For further discussion consult Chapter on Non-diabetic Melituria (Chap 29).

(*a*) LACTOSE.—($C_{12}H_{22}O_{11}$).—Lactose in the urine may give rise to confusion in the performance of Fehling's or Benedict's tests. Fortunately, the condition in which it characteristically occurs, namely, lactation, is usually known to the physician, and it is then not considered of significance It has also been found in the urines of nurslings Lactose, like glucose, reduces copper, is dextro-rotatory, but it yields a characteristic osazone with phenylhydrazine and is not fermented by pure yeast. However, the osazone is difficult to obtain from the urine and ordinary yeast is not to be depended upon for the fermentation test. Rubner's test and the mucic acid test for lactose are described in texts of laboratory procedures.

(*b*) PENTOSE.—($C_5H_{10}O_5$).—Pentoses, chiefly xylulose, are occasionally present in the urine. Pentose as well as levulose is more active than glucose in reducing alkaline copper solutions These ketoses reduce Benedict's solution at 50° to 60° C. in ten minutes and even at room temperature over a period of a few hours At boiling temperature the reduction by pentose [illegible] bath [illegible] also gi[illegible] Pentose is not fermented by yeast and is not optically active It may be detected by the Bial test

Orcinol—Hydrochloric Acid (Bial) Test.—Bial's reagent has the following composition

Orcinol	1 5 grams
Fuming HCl	500 grams
Ferric chloride (10 per cent)	20 to 30 drops

To 5 cc of the reagent in a test-tube add 2 to 3 cc of urine and heat the mixture gently until the first bubbles rise to the surface Immediately or upon cooling, the solution becomes green and a flocculent precipitate of the same color may form

To date we have recognized only 11 cases of essential pentosuria despite a constant search for such among patients with normoglycemic melituria (See page 733)

for pain of one kind or another, and, therefore, one must always be on the watch for this possibility.

As a routine procedure the sodium nitroprusside test should be performed on all urine specimens which give a red color with the Gerhardt test which does not fade upon boiling In this way acetone bodies masked by the "drug reaction" can be detected

2 *Acetone* —(CH_3COCH_3) —Folin[25] called attention to the fact that in strictly fresh urine containing "acetone bodies," the quantity of diacetic acid is nine or ten times that of acetone The older the urine, the greater becomes the relative proportion of acetone, because of the spontaneous degradation of the acetoacetic acid The Rothera test is much more sensitive for acetoacetic acid than for acetone

above

In recent years there have come into general use certain especially prepared nitroprusside reagents in powder or tablet form which permit the rapid detection of acetone in the urine[26]

3 *β-oxybutyric Acid* —($CH_3CH(OH)\ CH_2COOH$) – There is no simple qualitative test for β-oxybutyric acid

QUANTITATIVE TESTS —Although an idea as to the extent of ketosis in a patient with diabetes can be obtained by the examinations of the urine listed below, in the present day these are not commonly employed because (*a*) more accurate and informative data can be obtained from blood studies (see page 208) and (*b*) ketosis need be tolerated for only brief periods anyway, being quickly abolished by appropriate treatment with insulin and carbohydrate However, suitable urine tests are worthy of listing

1 *Reaction of Urine* —The most easily performed of the urine tests is concerned with its reaction The total titratable acidity is a good index of

[25] Folin Laboratory Manual of Biological Chemistry, 5th ed, New York, D Appleton-Century Company Inc p 211, 1934

[26] Such preparations are made by the Ames Co, Inc, Elkhart, Indiana, Brewer and Co, Inc, Worcester Mass and Denver Chemical Mfg Co Inc, New York, N Y

of the Benedict test. Of those met with in normal urine, creatinine and uric acid are the most common.

Glycuronic acid as such is not found in fresh urine, but conjugated glycuronic acids occurring in the urine spontaneously decompose and may cause confusion. Such conjugated glycuronic acids only appear after the ingestion of chloral hydrate, camphor, menthol, turpentine or phenol in large enough quantities to be of significance. If this point is borne in mind confusion will not arise. Glycuronic acid reduces copper and bismuth, but is not fermented by yeast. It may be difficult to detect in the presence of pentose, although one can rely on the characteristic osazone of pentose if differentiation becomes necessary.

The urine of individuals taking large doses of salicylates may give falsely positive tests for sugar. The confusion may be of real consequence in [illegible]

[illegible] droxyphenylacetic acid) which is present in the urine of such cases reduces [illegible]

through ammoniacal putrefaction. The urine may frequently be dark even when voided. We have not encountered alcaptonuria

Falsely positive urine tests for sugar and albumin have been reported in patients receiving massive doses of penicillin [24]

Methods for the Determination of "Ketone Bodies" in the Urine.— QUALITATIVE TESTS —1 *Diacetic Acid* (CH_3COCH_2COOH) —The simplest method for the detection of acidosis by urine examination is Gerhardt's ferric chloride reaction for diacetic acid (aceto-acetic acid). This test may be performed as follows:

[illegible]

Diacetic acid occurs in the urine in the same conditions as acetone and rarely is found except associated with acetone The latter represents diacetic acid from which in the process of degradation one molecule of CO_2 has been removed If very little diacetic acid is formed it may be entirely transformed into acetone, whereas if a larger quantity is produced, both acetone and diacetic acid may be present in the urine

It should not be forgotten that if a patient is taking salicylates, antipyrin, cyanates, or acetates, the foregoing test will give a somewhat similar reaction, but one that cannot be mistaken if the solution is boiled for two minutes Diacetic acid is unstable and any color it causes will disappear upon boiling, whereas the red color caused by any of the above substances does not disappear upon boiling Diabetic patients often take salicylates

[24] *Whipple and Bloom Jour Lab and Clin Med*, *36*, 635, 1950

We carry out routinely a quantitative estimation of the amount of albumin by a simple, rapid technique described by Kingsbury, Clark, Williams and Post.[29]

acid to

letting

that in standard tubes. It is much more satisfactory to express the amount

of urine rather than in the

ry slight trace, etc

of the kidneys in the first

to carry out tests of renal function such as the concentration and dilution test, phenolsulphonephthalein test, urea clearance test and blood non-protein (or urea) nitrogen determination

B. THE EXAMINATION OF THE BLOOD

Collection of Blood —Although we make extensive use of micro methods of analysis on capillary blood, we still employ venous blood on many occasions Such specimens have two distinct advantages over capillary samplings. (1) The only essential in the drawing of venous blood is that a sufficient quantity be put into a container where it is adequately mixed with an anticoagulant With capillary blood considerable skill and care are required to measure with a capillary pipette exactly 0 1 cc of blood with sufficient celerity to avoid clotting (2) When a larger quantity of blood is drawn as from a vein, determinations of more than one constituent of blood are possible on a single sample

Blood is ordinarily drawn from a vein in the antecubital space with the

are of 5 parts

approximate

neutral salt of

with sodium

fluoride will retain its sugar content at room temperature for at least several hours and for several days if kept in the refrigerator

[29] Kingsbury, Clark, Williams and Post Jour Lab and Clin Med, *11*, 981, 1926. The necessary apparatus may be purchased from R P Cargille, 118 Liberty St, New York, N Y

[30] Sherwood Ann Int Med *33*, 380, 1930

the amount of acidosis and runs parallel with the ammonia excretion. For details of the determination, consult standard laboratory texts.

2. *Ammonia.*—The quantity of ammonia in the urine is a measure of the reaction of the body to counteract the acidosis produced in it. To this extent its estimation gives a more accurate idea of the acid production of the body than any other of the urine tests at our disposal, which simply show the quantity of acid leaving the body. The test, however, becomes of less value as soon as extraneous alkali is administered, because under such conditions the ingested alkali is used by the body in preference to ammonia. The normal amount of ammonia nitrogen in the urine varies between 0.5 and 1 gram per day, and the ratio between the ammonia nitrogen and the total nitrogen in the urine is fairly constant at 1 to 25 (4 per cent). In severe diabetes the ammonia may gradually increase, and in Case 344 in pre-insulin days, it amounted to 8 grams in one day. The total nitrogen upon this same day was 19.2 grams, giving an ammonia nitrogen-total nitrogen ratio of 34.3 per cent. Ammonia may be determined by the permutit method as described by Folin and Bell.[27] This may be adapted for use with the photoelectric colorimeter or spectrophotometer.

3. *β-oxybutyric Acid.*—The tests for β-oxybutyric acid are all complicated, because they depend upon the extraction of the acid. However, in urine containing significant amounts of ketone acids, β-oxybutyric acid makes up about two-thirds of the total "acetone bodies" and may be determined along with the other ketone acids by a modification of Nanavutty's[28] blood acetone method. For further details, reference is made to original articles and standard laboratory texts.

Nitrogen.—The determination of the nitrogen in the urine is valuable because it furnishes an index to the quantity of protein which the patient is metabolizing. Incidentally, this is the easiest way to determine the quantity of protein in the diet, provided the calories utilizable are adequate. Since nitrogen constitutes 16 per cent of the protein molecule, one can multiply the quantity of nitrogen obtained in the urine by 6.25 to obtain the protein which it represents. One will not be far wrong if to this one adds 1 gram of nitrogen per day to offset the nitrogen of the feces, and considers this total quantity as representing the protein in the food. Formerly large quantities of nitrogen were obtained in the urine of diabetic patients, but insulin treatment and modern diets make the finding of excessive amounts rare, because abnormal tissue breakdown is prevented.

A daily analysis for nitrogen is time-consuming, but it is a simple matter to aliquot specimens of urine for a week and then obtain the average nitrogen excretion per day. If albumin is present in the urine, it must be *removed before the nitrogen determination is made.*

Simple methods by which the nitrogen in the urine may be determined may be found in standard laboratory texts.

Albumin.—The test for albumin in the urine should be performed at frequent intervals during the care of diabetic patients. The diagnosis of diabetes should not lead to neglect of the general treatment of the case

[27] Folin and Bell: Jour. Biol. Chem., 29, 329, 1917.
[28] Nanavutty: Ibid., 26, 1391, 1932.

Non-diabetic, doubtful, or borderline cases of glycosuria are not as uncommon as is sometimes thought. In 1937 a survey was made of 14,000 patients who had come for diagnosis or treatment of diabetes. Among [illegible]

TABLE 33.—COMPARISON OF NORMAL VALUES FOR BLOOD ELECTROLYTES EXPRESSED AS MILLIGRAMS PER 100 CC. AND AS MILLIEQUIVALENTS PER LITER

	Normal Range in	
Blood Constituent	*Mg./100 cc.*	*M eq./liter*
Sodium	313–333	136–145
Potassium	16–22	4.1–5.6
Calcium	9–11	4.5–5.5
Magnesium	2–3	1.7–2.5
CO_2 content	55–65 Vol./100 cc.	25–29
Chloride	350–390	95–105
Phosphorus	3–4	1.7–2.3
Sulfate	0.9–1.5	0.6–1.0
Protein	6.0–8.0 Gm./100 cc.	14.6–19.4

TABLE 34.—VALUES FOR ACID AND BASE CONSTITUENTS OF NORMAL HUMAN PLASMA

Acid	*M eq./liter*	*Base*	*M eq./liter*
HCO_3^-	27	Na^+	142
Cl^-	103	K^+	5
HPO_4^{--}	2	Ca^{++}	5
SO_4^{--}	1	Mg^{++}	3
Organic acids	6		
Protein	16	Total	155
Total	155		

It is not only in the matter of diagnosis, however, that blood-sugar tests are of tremendous value to the physician. Determinations, particularly of the fasting blood sugar, at intervals of months or years, afford a reliable index of the increasing or decreasing severity of the condition. Furthermore, in patients using crystalline insulin exclusively, or in those taking NPH or lente insulin before breakfast, the level of the fasting blood sugar will indicate whether or not a bedtime dose of insulin would be beneficial. For patients taking protamine zinc insulin once daily before breakfast, the [illegible]

The employment of an anticoagulant which inhibits glycolysis and helps to preserve the sugar content of blood deserves much wider use. In this way blood sugar determinations may be made at various times of the day without the necessity of immediate processing of the blood The whole [illegible]

for periods up to 6 days, even though the blood sugar samples were kept at room temperature.

When blood is withdrawn for a determination of the carbon dioxide content of the plasma (blood taken under oil) or for a determination of blood cholesterol or fat a satisfactory anticoagulant is potassium oxalate. In this instance the blood should be analyzed promptly, particularly if the sugar content is desired. For special determinations there are special indications as to the drawing of the blood

For most determinations of blood constituents in which colorimetric comparisons are employed, the photoelectric colorimeter is recommended for accuracy and speed

Units of Measurement of Blood Electrolytes.—It is preferable to express values for electrolytes in the blood in terms of chemical equivalence, *i.e.*, milliequivalents per liter, rather than as milligrams per 100 cc , since only in this way can their relative magnitude and interrelationship be evaluated properly The figure for milliequivalents per liter is obtained by use of the following formula

$$\frac{\text{No. of mg. per 100 cc.} \times \text{valency}}{\text{Atomic wt}} \times 10 = \text{milliequivalents per liter}$$

Thus, to convert a plasma chloride value of 355 mg per 100 cc. to milliequivalents, one proceeds as follows:

$$\frac{355 \times 1}{35.5} \times 10 = 100 \text{ milliequivalents per liter}$$

In Table 33 is shown the normal range of blood electrolytes expressed in milligrams per 100 cc and as milliequivalents per liter In Table 34 illustrative values for acid and base constituents of normal human plasma are shown and in Figure 21, page 380 electrolyte patterns for extra- and intra-cellular fluid are shown

Blood Sugar.—Without a knowledge of the blood sugar both the diagnosis and the treatment of a patient with sugar in the urine have an un- [illegible]

Kantor and Wilkerson Diabetes, 6, 176, 1957

Non-diabetic, doubtful, or borderline cases of glycosuria are not as uncommon as is sometimes thought. In 1937 a survey was made of 14,000 patients who had come for diagnosis or treatment of diabetes Among this group it was found that 14 8 per cent had glycosuria of a non-diabetic type as shown by determination of the blood sugar In diagnosis, particularly in mild cases, blood sugar determinations one hour after a meal are preferable to those made with the subject in the fasting state.

TABLE 33 —COMPARISON OF NORMAL VALUES FOR BLOOD ELECTROLYTES EXPRESSED AS MILLIGRAMS PER 100 CC AND AS MILLIEQUIVALENTS PER LITER

	Normal Range in	
Blood Constituent	*Mg /100 cc*	*M eq liter*
Sodium	313–333	136–145
Potassium	16–22	4 1–5 6
Calcium	9–11	4 5–5 5
Magnesium	2–3	1 7–2 5
CO_2 content	55–65 Vol /100 cc	25–29
Chloride	350–390	95–105
Phosphorus	3–4	1 7–2 3
Sulfate	0 9–1 5	0 6–1 0
Protein	6 0–8 0 Gm /100 cc	14 6–19 4

TABLE 34 —VALUES FOR ACID AND BASE CONSTITUENTS OF NORMAL HUMAN PLASMA

Acid	*M eq liter*	*Base*	*M eq liter*
HCO_3^-	27	Na^+	142
Cl^-	103	K^+	5
HPO_4^{--}	2	Ca^{++}	5
SO_4^{--}	1	Mg^{++}	3
Organic acids	6		
Protein	16	Total	155
Total	155		

It is not only [illegible]
are of tremend[illegible]
of the fasting bl[illegible]
index of the increasing or decreasing severity of the condition Furthermore, in patients using crystalline insulin exclusively, or in those taking NPH or lente insulin before breakfast, the level of the fasting blood sugar will indicate whether or not a bedtime dose of insulin would be beneficial For patients taking protamine zinc insulin once daily before breakfast, the

given before breakfast. Likewise, the blood sugar level in the late afternoon (along with the fasting value) serves as a guide to the proper and safe dosage of NPH, lente or globin insulin. In this way hypoglycemia and consequent insulin reactions may be foreseen and patients be spared the inconvenience caused by them. In the treatment of diabetic coma a knowledge of blood sugar values is almost imperative.

An ideal blood sugar method should meet the following requirements: (1) It should determine only glucose, eliminating other copper reducing substances, chiefly glutathione, ergothionine and creatinine, which usually account for Folin and similar procedures. Unfortunately, the amount is variable and Mosenthal[32] found quantities of non-glucose substances as great as 80 mg. per 100 cc ; (2) it should be adaptable for both macro- and semi-microtechniques, (3) the reagents should include chemicals which are relatively inexpensive and not overly hazardous to technicians, such as cyanide solutions or concentrated sulphuric acid, (4) the method should require a minimum of time, technique and apparatus; (5) it should be accurate and yield reproducible results. One procedure which fulfills these requirements quite well is the Nelson modification of the Somogyi method.[33,34] This is a method designed for large quantities of blood, however, it can be adapted for use with 0.1 cc. amounts with only minor changes in reagents and procedures. In the laboratories both at our office and at the New England Deaconess Hospital the Somogyi-Nelson method has been used routinely for the past few years.

The use of capillary blood often is desirable, particularly in children, in patients such as those in diabetic coma from whom frequent samples of blood for sugar determination are helpful and in those patients whose veins, either because of nature or because of medication, are difficult to puncture. If care is used in taking the blood samples and in performing the analyses, results which can be readily duplicated may be easily obtained. In interpreting results obtained on capillary blood, it must be remembered that whereas in the fasting state, the sugar content of capillary and venous blood is approximately the same, after a meal or after glucose the capillary values are (in the normal person) 20 to 50 milligrams higher than the corresponding figures on venous blood. (See page 156.)

Cholesterol and Total Lipids. - Accurate analyses of the fat of the blood and particularly partitive studies of the various lipid fractions are time-consuming, and for that reason cannot be made a part of the routine investigation of a patient by most physicians. Nor would such seem to be necessary, because only 93 of 2200 patients studied as long ago as 1929–39 showed blood cholesterol values of 400 mg. per cent or more. This was all the more significant because the determinations had, for the most part, been done only in instances in which it was thought possible that abnormal values might be revealed. Our clinical impression of our untabulated experience since 1939 is in essential agreement, except during periods of poor

[32] Mosenthal. Loc. cit., p. 155.
[33] Nelson. Jour. Biol. Chem. *153*, 375, 1944.
[34] Somogyi. Ibid., *160*, 61, 69, 1945.

control of diabetes, the blood cholesterol is within normal limits (150–250 mg. per 100 cc.) in the vast majority of patients

We use the methods of lipid analysis designed by Bloor[35] and his associates in which the determination of total fat is made by iodometric titration following oxidation by dichromate in the presence of concentrated sulphuric acid Fortunately the amount of cholesterol in the blood ordinarily gives a good index as to the status of fat metabolism Consequently, one may carry out this determination alone In clinical work we employ [illegible]

of the total cholesterol,[36] in cases of hepatic insufficiency the percentage may be reduced considerably even to complete disappearance of the ester fraction [37]

Rivin, Yoshino, Shickman and Schjeide[37a] have called attention to the wide variation in results which may be observed for serum cholesterol when determinations are carried out in different laboratories

Carbon Dioxide in Blood Plasma.—Whether in health or in disease, the reactions of the body remain nearly constant and the blood not only con- [illegible]

and (3) by saving of alkali through the excretion of acid phosphate through the kidneys

The blood plasma normally contains a certain amount of bicarbonate ($NaHCO_3$) An idea of the amount can be obtained by measuring the quantity of CO_2 which is set free when a stronger acid, such as sulphuric acid or lactic acid, is added to the blood The CO_2 thus obtained ("CO_2 content") is expressed as milliequivalents (m eq) per liter or, less desirably, as volumes of CO_2 per 100 cc of blood (volumes per cent) Normal venous blood contains from 25 to 29 milliequivalents per liter (55 to 65 volumes per 100 cc) of CO_2

[illegible]

*(55 and 75 volumes per cent) Both the CO_2 content and the CO_2 com-*bining-power of the blood are measures of alkalinity We routinely use the standard method of Van Slyke[38] for determination of the carbon dioxide content of the plasma, collecting blood samples under oil

[35] Bloor Jour Biol Chem , 77, 53, 1928
[36] Sperry and Schoenheimer Ibid , *110*, 655, 1935
[37] Epstein Arch Int Med *50*, 203, 1932
[37a] Rivin *et al* Jour Am Med Assn , *166*, 2108, 1958
[38] Van Slyke Jour Biol Chem *30*, 347, 1917 Van Slyke and Stadie Ibid , *49*, 1, 1921

The Hydrogen-ion Concentration of the Blood.—Human blood is slightly alkaline with normally a pH of about 7.35. In severe diabetic coma the value may fall to just below 7.0 In artificially produced acidosis in dogs the pH may fall as low as pH 6.9 A reaction of pH 7.6 or higher may be obtained after the administration of alkalies. The buffer action of the carbonates of the plasma and the protein of the whole blood enables the blood to take up considerable amounts of acids or alkali without appreciable change in hydrogen-ion concentration. Until practically all the plasma [illegible] pH of the [illegible] the deter- [illegible]

Acetone in the Blood.—It sometimes occurs that acidosis is present but is not disclosed by the simple ferric chloride and sodium nitroprusside tests for diacetic acid and acetone in the urine. Under such circumstances a qualitative test for acetone in the blood may be made. In certain situations this may allow differentiation between ketosis and other forms of acidosis Furthermore, the degree of response of a positive reaction serves as a guide to the severity of ketosis and to treatment. The rough estimation of the amount of acetone in plasma in patients with diabetic coma or suspected coma should be carried out at once when the patient is first seen.

Method for Detection of Aceto-acetic Acid and Acetone in the Blood — The blood is drawn into a syringe or tube containing a few crystals of potassium oxalate, then centrifuged for five minutes at medium speed. The test is made on the plasma with as little delay as possible, as there may be some loss of acetone on standing If plasma must be kept for future testing, it should be placed in the refrigerator in a stoppered tube.

Dilutions of the plasma are made with water so that one has 4 tubes containing the following:

- Undiluted plasma
- 1 2 dilution 1 part plasma, 1 part water
- 1 4 dilution 1 part plasma, 3 parts water
- 1 8 dilution 1 part plasma, 7 parts water

Four small mounds of powder ("Acetone test-Denco"[39]) or 4 "Acetest" tablets[40] are arranged on a flat, white surface so that one mound of powder or one tablet corresponds with each of the 4 tubes Two drops of plasma or plasma dilution are added to the test material Results for each of the 4 tests are graded as O, +, ++, +++, ++++, depending on the depth of the color produced which in positive instances [illegible]

cent solution of sodium nitroprusside and 2 drops of concentrated ammonium hydroxide Thoroughly mix (One may instead overlay with the ammonium hydroxide and then without shaking the tube, observe any color reaction at the junction of the two liquids) If the test is positive, in from one to ten minutes a color develops which varies from a pale lavender to a deep permanganate hue, in this way indicating whether little or much acetone is present

Quantitative Estimation of Acetone in Blood —We have found satisfactory Nanavutty's[41] titrimetric modification of Van Slyke's gravi-

[39] Made by Denver Chemical Manufacturing Co , Inc , New York 13, N Y
[40] Made by Ames Co , Inc , Elkhart, Indiana
[41] Nanavutty Loc cit p 202

metric method for the determination of "total acetone bodies" in the blood and urine. This method is applicable to quantities of blood as small as 0.5 cc but cannot be used with accuracy for amounts of acetone under 5 mg per 100 cc. The highest value that we have found so far in diabetic coma has been 198 mg per cent. In normal individuals values approaching zero are found. A more sensitive method is that of Greenberg[42] as modified by Boshell.[43]

Non-protein Nitrogen.—In recent years as the number of patients with diabetes of long duration has increased, the incidence of nephropathy has become greater. From January 1, 1950 to December 11, 1957, of 5016

Chlorides.—As in the case of urine, the determination of the chlorides in the blood gains importance from the fact that the water and electrolyte content of the body in diabetes may vary rapidly and widely. This is in addition to the value which such determinations have in the management of cases of nephropathy and hypertension in connection with diabetes. A low plasma chloride is seen chiefly in diabetes in connection with acidosis when chloride is lost from the body through vomiting or through excretion in the urine. It is also encountered in so-called "salt-losing nephritis" seen in association with diabetes.

The method used in the laboratory of the New England Deaconess Hospital is that of Van Slyke and Sendroy.[44]

Total Protein.—A knowledge of the total protein and albumin and

nephropathy with marked albuminuria, azotemia, edema, hypertension and retinitis, has presented a difficult problem. Edema is often accompanied by low serum protein values with reversal of the albumin-globulin ratio. In the determination of the serum protein we have used the method of Kingsley[45] with success, although it has seemed important that the plasma or serum used be clear and not turbid as with blood containing large amounts of lipid material. In the laboratory at the New England Deaconess Hospital, the Kagan[46] falling drop technique is used for the determination of serum protein.

Total Base, Sodium and Potassium.—Not infrequently, particularly in patients under treatment for diabetic coma, a knowledge of the sodium and potassium content of the blood is of great value. For the determination of these constituents of the blood serum, a flame photometer is necessary

[42] Greenberg: Jour. Biol. Chem., 154, 177, 1944.
[43] Boshell, Renold and Zahnd: Submitted for publication.
[44] Van Slyke and Sendroy: Jour. Biol. Chem., 58, 532, 1923.
[45] Kingsley: Ibid., 133, 731, 1940.
[46] Kagan: Ibid., 17, 369, 1938; Ibid., 17, 373, 1938.

since other analytical methods are unsatisfactory, laborious and time-consuming. By measuring the intensity of the light produced with solutions of known concentration and preparing a calibration curve of intensity versus concentration, the sodium or potassium content of other solutions may subsequently be determined by making use of the curve.

Carotene.—Certain diabetics may retain ingested vegetable pigments to a greater extent than do normal individuals and a characteristic yellow discoloration of the skin, most noticeable on the palms and soles, may be produced. One finds in such cases an increase in the carotene content of the blood. The occurrence of this abnormality is commonly held to be due to the fact that diabetics as a group are apt to use more vegetables in the diet and that in certain diabetics there is, to a greater or less degree, an inability of the liver to convert carotene to vitamin A as normally occurs,[47 48] although Lembrechts, Leleux and Thomas thought carotenemia to be of alimentary origin.[49] Clinical experience has shown that the condition is compatible with good health. It may be remedied by reducing the amount of carrots and other carotene-containing vegetables, butter and egg yolk in the diet. From a study of the carotene content of the blood plasma of 24 normal and 32 diabetic individuals, Mosenthal and Loughlin[50] concluded that the majority of diabetics today, in contrast to former times, have plasma carotene and vitamin A levels that are within normal limits. This agrees with our clinical impression although we have made no systematic observations. This experience suggests that more adequate control of the [illegible]

[47] Ralli, Pariente, Brandaleone and Davidson Jour Am Med Assn, *106*, 1075, 1936 See also Ralli, Brandaleone and Mandelbaum Jour Lab and Clin Med, *20*, 1266, 1935

[48] Stueck, Flaum and Ralli Jour Am Med Assn, *109*, 343, 1937

[49] Lembrechts, Leleux and Thomas Acta med Scandinav, *116*, 11, 1943

[50] Mosenthal and Loughlin Jour Mt Sinai Hosp, *12*, 523, 1945

[51] Connor Jour Biol Chem, *77*, 619, 1928

Chapter 8

THE DEFINITION, DIAGNOSIS, CLASSIFICATION, SYMPTOMATOLOGY AND PROGNOSIS OF DIABETES

ELLIOTT P JOSLIN, M.D.

A. DEFINITION

DIABETES is a chronic hereditary disease, characterized by an increase of glucose in the blood and the excretion of glucose in the urine, it is

endocrine glands other than the pancreas, particularly the pituitary, but also the adrenal and thyroid

B. THE DIAGNOSIS OF DIABETES

If a patient has sugar in the urine, it is a safe rule to consider the diagnosis to be diabetes until the contrary is proved The use of the term glycosuria begets indifference and may lead to disaster Patients with glycosuria

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judged by information obtained by means of an intensive follow-up program over many years of time Many clinicians depend upon the value at the end of two hours after a meal, but such a value is unreliable Its significance depends upon its comparison with the value before the meal, the rapidity of absorption of the meal, and the time spent in taking the meal

[1] Folin and Wu Jour Biol Chem, 38, 81, 1919, 41, 367 1920

But we warn here, as elsewhere in this book, that dependence upon blood-sugar tests must be subject to cautious and critical analyses. One swallow does not make a summer. For a discussion of normal blood-sugar values and blood-sugar tolerance tests, see pages 161 and 206, and also Wilkerson and Krall[1] *who in a follow-up of sub-diagnostic cases found diabetes 8 times* as common as in a comparable unselected series.

Errors in diagnosis as disclosed by years of subsequent observation are most commonly due to the use of a single abnormal blood sugar value reported by *the patient or found in our own laboratory even in connection* with glycosuria. All such values should be verified, and particularly so if the glycosuria is under 1 per cent. It is extraordinary for a glycosuria of 2 per cent or more, save in the case of renal glycosuria, to be unassociated with diabetes *All in all it is safer to err in diagnosing a case to be a diabetic* than a non-diabetic. In both instances the patient and his family blame you, but in the latter in addition your own soul Repeatedly we [illegible]

[illegible] more than formerly one is apt to consider them borderline cases with a prediabetic tendency (See p 36).

As *true diabetics* are classified all patients whose venous blood sugar on an unrestricted diet is 130 milligrams per cent or more fasting or 170 milligrams per cent or more after a meal with simultaneous glycosuria which is plainly related to diet. Glycosuria is considered essential for the diagnosis of diabetes. By holding to this principle one avoids snares which hyperglycemia alone often sets in the form of a high renal threshold, as in certain aged people or in individuals with certain chronic diseases. *Potential diabetics* are those with glycosuria closely related to the diet who easily become sugar-free with slight restrictions, but whose blood sugar is below [illegible] milligrams per [illegible] give up the [illegible] very few as [illegible] ce fresh zeal to recognize them and new hope to avert frank diabetes are aroused. An explanation of their small number of late is that we have more assiduously tried to force new cases into the diabetic or unclassified glycosuric groups and have often postponed a diagnosis for this purpose for days, weeks or even months *Renal glycosurics* are individuals who have shown a constant glycosuria, irrespective of diet, for years, are symptomless, and have a blood sugar which is invariably normal The *unclassified glycosurics* form a heterogeneous class and undoubtedly include many cases of so-called alimentary glycosuria, cases with a low renal threshold, chance glycosurias in the course of infections, incipient, potential diabetics and others associated with organic disease of the pituitary and hypothalamic regions, thyroid, *adrenals, liver,* biliary *tract and* pancreas These cases form a

[1] Wilkerson and Krall Loc cit p 35

[2] John Am Jour Digest Dis, *17*, 219, 1950

dangerous group They constitute about 15 per cent of all glycosurics coming for treatment. One never rests easy with an "unclassified" glycosuric. Such a diagnosis worries the doctor, annoys the patient, and exasperates insurance agents Yet, as pointed out repeatedly, this may be "the very stone which the builders rejected, but became the head of the corner." (See p 212) With assiduous treatment we may have averted frank diabetes in later years For Lipoatrophic Diabetes, See page 217

A positive Benedict test may be shown by patients other than those above mentioned, and it is only treating them fairly to prove, if the blood

tolerance test is unavoidable at times, but routine reliance solely upon

'he glycosurias is undesirable

ymptomatology and physical

It is not always wise or just to the patient to complete the diagnosis at

sugar-tolerance test with 100 grams glucose can be performed after the patient has lived for five or more days on a free diet containing for an adult at least 250 grams of carbohydrate daily A sugar-tolerance test is by no means to be considered as law and gospel in and of itself The previous diet or the presence of an infection may invalidate it (See pages 160 and 165)

If another physician has diagnosed diabetes in the past, but urine and blood are normal at the time of the first visit to us, we are loath to perform a glucose tolerance test unless and until it appears absolutely necessary to

f all, the insulin is gradually reduced,

when these procedures fail to disclose

employed Insulin is never omitted

unless one has assuranc

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statements to the contrary until time and study have yielded unequivocal data

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It showed that between the years 1900 and 1935, 9 9 per cent of 1946 patients originally thought non-diabetic were subsequently found to have

[1] Marble *et al* Am Jour Med Sci, *197*, 533, 1939

developed diabetes. Obviously a certain percentage of individuals, not actually showing diabetes upon the day of examination, will develop it in the course of ten to thirty years, and so the error represented by this percentage is above rather than below the true value. Diagnostic errors of commission also have been studied. The death certificates of our patients later dying under the care of other physicians have been investigated.[5]

Recent study has shown that only 33 per cent of individuals dying with diabetes have been so classified, while 41.2 per cent have been certified as dying of other diseases although diabetes is mentioned in the death record, and 2.8 per cent failed to have the disease mentioned on the record (See p. 22)

If diabetes is detected early, it is far more susceptible to treatment. The fact that the development of diabetes in a dog as a result of injections of anterior pituitary extract can be prevented by the administration of insulin[6,7] emphasizes the need for prompt and energetic treatment of a case as soon as the diagnosis is made. Naunyn firmly believed in this, and so do we. Unfortunately the interval between onset and diagnosis is far too great, and this will be lessened only by more frequent routine examinations of the urine. The only way in which an early diagnosis of diabetes will ever be made is to search for it. It is far easier to diagnose than tuberculosis or cancer.

Blotner's[8] surveys of selectees at the Boston Induction Center, the studies upon the incidence of diabetes conducted by the U. S. Public Health Service Diabetes Detection Drives (see page 35, also page 36) and Grott's[9a] studies in Lodz, Poland, show how many diabetics largely symptomless, can be brought to light. Only the persistent examination by physicians of all patients coming to them will reveal the disease, and these examina-

schools, colleges, all public institutions, transportation units of all kinds, and manufacturing plants, in police and fire departments, just as such examinations are carried out by insurance companies, and one cannot emphasize too strongly the advantage of the latter following up their policyholders by a yearly examination of those who are susceptible to diabetes. Everyone should have the urine examined on his or her birthday. Start the custom with the children and it will persist to old age. The urine should be tested before departure from a hospital as well as at entrance, and no physician should discharge a patient following acute disease or childbirth without making an examination of the urine for albumin and sugar.

March 30, 1920, there came to our office a woman with diabetes. She was given the usual examination with suggestions for treatment, and as it was impracticable for her to enter the hospital, she was taught on the spot

to examine her urine She went home and shortly after contracted pneumonia and died But in the intervening days amid her household cares

this story At the time she learned the Benedict test and made these urine examinations for her friends, Louisa Drumm, Case 1796, was seventy-nine years and four months old

as diabetic conscripts The physician should consider it as important to protect his patients from acquiring diabetes as he feels it incumbent on himself to vaccinate them against smallpox, diphtheria, typhoid fever, tetanus and polio, or to protect them from exposure to tuberculosis

C METHODS OF CLASSIFICATION OF SEVERITY OF DIABETES

No methods for the classification of diabetics or determination of the severity of the disease to my mind are satisfactory. This must of necessity be so if the conception of the unity of diabetes is correct No sooner are the boundary lines drawn than one case after another like sheep will break through the fence The severe case with advancing years grows mild, the mild case in childhood as it passes through puberty may become severe only

The func-

becomes

, *or severe*

largely as the doctor with his diet, insulin and exercise makes him (See page 256, Case 8095.) The patient need not necessarily progress through the stages of mild, moderate, and severe diabetes, although Foglia's* 95 per cent depancreatized rats did just this For the first two months they showed no diabetes, in the next two to four months they exhibited incipient diabetes with glycosuria after ingestion of carbohydrate, but in six months they became frankly diabetic with all the symptoms and signs and complications

This whole question of the classification of the diabetic is involved in the more important one of the unity of diabetes, but before discussing that more important topic former methods of classification may be mentioned because they have often served a useful purpose

Early in the century an estimation of the tolerance for carbohydrate was employed to classify the patients Severe diabetics were those who showed glycosuria with less than

severe diabetics were the

were considered mild S

scribed in protein and fat and particularly in total calories that such classifications would break down Furthermore, Benedict and Joslin, like

* Foglia Proc Am Diabetes Assn, 6, 513, 1946

von Noorden, agreed that no diabetes was 100 per cent. The discovery of insulin made obsolete such a classification.

The units of insulin required to control the disease at first appeared to be a means of differentiating the types of diabetes, but here again the accessory factors useful in treatment, such as details of diet and exercise, broke up such a plan. It was not easy to determine who was sensitive and who was not sensitive to insulin because as time went on such barriers were broken. Perhaps new methods of differentiation will become available because of the reactions of patients to oral medication.

Wrenshall's demonstration of the presence of insulin in the pancreas up to 60 per cent of the normal in the middle-aged, well-nourished diabetic patient and its absence in children, fits in with the above conception, but against it is the clinical remission of the young and aggressively treated diabetic, particularly a child, as described by Brush.[10] During the remission the child must have insulin in his pancreas but how can one explain it? As yet data are lacking for the insulin content of the pancreas in these children for this period of remission. One would like to know also the insulin content of the blood but there, too, the data have not been available. It is regrettable that Bornstein[11] could not examine the remission cases of Brush and indeed, that a simple method for insulin assay of the blood was not then available.

Recently an opportunity has been afforded us to learn the insulin content of the blood in a case of remission The method used by Renold and Martin is described on page 142. This patient, Case number 50845, 19 years old, was rescued from coma in December, 1957 Under the treatment of Drs Buckley, Sieracki, and Cadigan, 1600 units of insulin were required A montl [illegible]
while [illegible]
reduce [illegible]
Renold and Martin. The results of this assay are expressed in microunits (1 millionth of a unit) of insulin-like activity per millileter of plasma. The normal value is approximately 8–250 microunits per liter but she showed [illegible]

per liter A case like this indicates how difficult it is to classify diabetics On this day the urine after breakfast was sugar free and the blood sugar by the "true" glucose method, 177 mg

The French Methods.—The older French clinicians divided their cases into two classes (*a*) *Diabète gras* and (*b*) *Diabète maigre*, and immediately the picture of the old, mild, fat diabetic and the young, severe, thin patient comes to mind Yet time and treatment destroy the grouping because on the one hand the thinnest of the severe thin may have been at one time the fattest of the mild fat, and the uncontrolled fat girl of severe type in her middle teens may once have been a slim diabetic easily amenable to treatment when first seen at seven years, and again later may change back to a

[10] Brush Am Jour Dis Child, 67, 420, 1944
[11] Bornstein Jour Exp Biol Med Sci, 28, 87, 93, 1950

much less severe diabetic at twenty years of age With control of the disease and the element of time, the tolerance for carbohydrate changes, as well as the units of insulin required, as determined by Falta and Himsworth (See page 151) The same holds true for acidosis

A third type of diabetes described by R. D. Lawrence[12] is most unusual and he termed it "Lipoatrophic Diabetes." Fortunately, a series of cases has been assembled by Renold and Schwartz and to them we are greatly indebted for the following account of this unusual condition based on 9 cases

Lipoatrophic Diabetes.—This syndrome, although rare, may provide important clues concerning factors affecting the pathogenesis and the symptomatology of diabetes mellitus The syndrome was first described by Lawrence[13] in 1946, in a 26-year old woman with pre-existing diabetes Since that time a total of nine cases has been reported in the literature, as summarized in Table 35. Characteristically, the syndrome includes: (1) total lipoatrophy, with complete lack of subcutaneous adipose tissue; (2) marked hepatosplenomegaly (with increased storage of lipid, disruption of lobular architecture, progressive fibrosis) with often surprisingly adequate *hepatic function; (3) diabetes with mild to moderate insulin "resistance,"* requiring up to 2000 units for control; (4) no tendency to ketoacidosis, (5) hypermetabolism without hyperthyroidism, (6) frequently hyperlipemia and (7) mild hirsutism

The data in Table 35 has been compiled and made available to us through the kindness of Dr Robert Schwartz of the Children's Medical Center in Boston Some cases were collected previously by Dr R D Lawrence[14] Case 9 has been followed for many years at the Children's Medical Center

guese descent is presently 14 years old, and developed hepatomegaly be-

of the cellular architecture in the second instance Liver function tests were surprisingly normal throughout, and have remained so Both growth and skeletal maturation were accelerated, facts which have been emphasized by Dr Schwartz, who also found evidence of increased growth in other reported cases Diabetes mellitus developed at age 12 years and has been characterized by marked glucosuria, up to 100 grams daily, and by remarkable resistence to ketoacidosis Insulin requirements varied at around 200 units per day Mild hypermetabolism has been noted, although not consistently, and moderate hirsutism was present as early as age 19 months

[12] Lawrence Proc Roy Soc Med , Sect Endocrinol , *43*, 355, 1950 Brit Med Jour *1* 563, 1951

[13] Lawrence Lancet, *1*, 724, 773, 1946

[14] Lawrence Ann Int Med , *43*, 1199, 1955

It is of interest to note that lipoatrophy may precede diabetes and, *vice versa*. Lawrence first suggested the possibility that the syndrome might represent in part the metabolic consequences of the absence of adipose tissue as a major site of glucose disposal as well as a major site of insulin action. Thus, the unavailability of a tissue responsible for a large proportion of glucose metabolism after a glucose load might lead to glucose accumulation in the blood stream, to increased insulin requirement in order to dispose of the glucose in other tissues, and perhaps sooner or later to a diabetic syndrome. *It is noteworthy in this respect that the hepatomegaly* with increased lipid content might be interpreted, at least in part, as functional substitution of fat storage in the liver for the usually predominant fat storage in adipose tissue. The possibility of adrenal dysfunction in these patients has also been suggested, although not established, and Dr. Schwartz' observations of frequently accelerated growth suggests a tentative relation of the pituitary gland to at least some feature of the disorder It has not been possible to demonstrate the presence of circulating insulin "antifactors" capable of inhibiting the activity of insulin in the presence of adipose tissue in the patient studied in Boston (Case 9).

Although the etiology and pathogenesis of the syndrome remain to be clarified, and many additional observations on these patients remain to be made, special emphasis has been given this group here, because of the possible theoretical importance of the syndrome. We may well learn from the combination of lipoatrophy and diabetes significant facts relating to the role of endocrine and metabolic factors concerned with adipose tissue physiology and the diabetic state.

Insular and Extra-insular.—Umber[15] refers *frequently* to insular and extra-insular diabetes, but in general he uses the terms to differentiate between true diabetes and the glycosurias We agree with Marañon[16] that one cannot draw a sharp distinction along these lines. Sometimes the hypophysis, thyroid or adrenals are primary and the pancreas secondary, and so the pancreas may compensate for the others

For attempts to distinguish various types of diabetics according to their reactions to insulin and to evaluate hepatogenous and tissue resistance, see pages 215-217 Also see pages 125 and 127 for the milder types of

[illegible]

that the disease revolved around the pancreas Heredity like a red thread

[illegible]

became severe The authors share Naunyn's belief, of course recognizing the many influences, then unknown, which affect diabetes, such as those contributed by the anterior pituitary, adrenal, and thyroid glands, and the

[15] Umber Handbuch der gesamten Unfallheilkunde, Stuttgart, Ferdinand Enke, vol *1*, 1932

[16] Marañon Med Klin, *31*, 42, 1935

TABLE 35.—LIPOATROPHIC DIABETES[1]

	Sex	Age	Onset Lipoatrophy	Growth	Diabetes Sugar	Diabetes Ketones	Diabetes Insulin	Lipemia Gm Per Cent	Cirrhosis	BMR
1	F	27	15	?	Tr	0	0	0	+	+59
2	M	4 9	4	N?	+++	0	284	+	+++	N
3	F	26 34	26	?	+++	±	2,000	9 0	++++	+170
4	F	12 16+	10 mo	?	+++	0	0 diet	4 0	++	+45
5	F	13 16+	13	?	+++	0	2,000+	12 5	++	+30
6	F	20 mo 6	20 mo	Inc	0	0	—	1 1	+	+44
7	M	6	? 2½	Inc	++	0	—	1 2	+++	?
8	M	2	? 6 mo	Inc	+	0	—	1 9	+++	?
9	F	4 mo 14	4 mo	Inc	+++	±	200U diet	1 3	+++	+20

[1]Data supplied by Albert E. Renold, M D and Robert Schwartz, M D

It is of interest to note that lipoatrophy may precede diabetes and, *vice versa*. Lawrence first suggested the possibility that the syndrome might represent in part the metabolic consequences of the absence of adipose tissue as a major site of glucose disposal as well as a major site of insulin action. Thus, the unavailability of a tissue responsible for a large proportion of glucose metabolism after a glucose load might lead to glucose accumulation in the blood stream, to increased insulin requirement in order to dispose of the glucose in other tissues, and perhaps sooner or later to a diabetic syndrome. It is noteworthy in this respect that the hepatomegaly with increased lipid content might be interpreted, at least in part, as functional substitution of fat storage in the liver for the usually predominant fat storage in adipose tissue. The possibility of adrenal dysfunction in these patients has also been suggested, although not established, and Dr. Schwartz' observations of frequently accelerated growth suggests a tentative relation of the pituitary gland to at least some feature of the disorder. It has not been possible to demonstrate the presence of circulating insulin "antifactors" capable of inhibiting the activity of insulin in the presence of adipose tissue in the patient studied in Boston (Case 9).

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The Unity of Diabetes.—Naunyn believed in the unity of diabetes and

his first visit as being severe, if rigor... whereas, the apparently mild case ... became severe The authors share ... the many influences, then unknown, which affect diabetes, such as those contributed by the anterior pituitary, adrenal, and thyroid glands, and the

[19] Umber Handbuch der gesamten Unfallheilkunde, Stuttgart, Ferdinand Enke, vol *1*, 1932

[20] Marañon Med Klin, *31*, 42, 1935

upon death certificates, but for such a purpose both are unreliable. The diabetic patient a generation ago lived so short a time and his career was so tragic, particularly in childhood, that it was natural to record the onset as "acute" and the end as "acutely fatal." It may be said that "acutely fatal" diabetes is a diabetic ghost which, like another of its kind, "complete diabetes," has vanished from medical nomenclature.

The latency of diabetes is illustrated by its development in a parent, or

illustrative of the action of the growth hormone In cases in which it came on almost as an apoplectic stroke the circumstances were varied

Examples of allegedly acute onset which stand out in my memory are Case 7, the man who was injured by a bull, Case 10, the Boston bank clerk, whose diabetes came on during an important and unaccustomed mission while turning a corner in New York City, Case 5786, the boy who fell through the ice and was rescued by his dog Yet I could not take oath that these patients were free from sugar even a few days before the assigned date Moreover, the records of these cases were taken by me in 1898, 1899 and 1927 respectively,

less critical charact

and glycosuries is

similar case observed by Wilder

It will be worth while to endeavor to learn more accurately the type of onset of diabetes It will furnish assistance in a search for the etiology and will raise queries in the minds of the pathologists, it should indicate the character of the methods which must be adopted for prevention, it may be of value in classification and prognosis, and even treatment [20]

In an effort to verify former data, Dr Robert F Bradley and the senior author in 1952 studied 100 cases with onset at seventy years or above and obtained data which suggests that the onset in these decades is less frequent than ordinarily conceived This is shown in various ways First, because none of the cases were stated as of sudden or rapid onset although the average age at onset for the 100 cases was 74 5 years, and only 0 3 years elapsed until the diagnosis was made, and, second, in 47 instances onset and diagnosis were recorded as identical, thus implying that the history taker was not impressed with rapidity of onset and evidently at a loss about the period of duration before the diabetes was diagnosed The average age at the first visit was seventy-six years My oldest diabetic, Case 52560, born August, 1857, first seen November, 1958, aged 101, was known to be sugar free

[17] Jackson Jour Clin Endocrinol and Metab 14, 174 1954
[18] Young Loc cit, p 69
[19] Sprague Diabetes Mellitus, in Tice's Practice of Medicine Hagerstown, Md, W F Prior Co, Inc, vol 9, p 85a 1945
[20] Smith and Grishaw Arch Int Med 67 465 1940

liver, and temporarily by the character of the diet, exercise, infections, and acidosis. Complete pancreatectomy in a rat produces diabetes

D. THE SYMPTOMS OF DIABETES

Onset of Diabetes.—I have little confidence in data purporting to give the onset of diabetes. A woman born in 1899, Case 50844, weight in 1921, 111 pounds, showed glycosuria during her first pregnancy in 1938, at age 39, when she weighed 180 pounds. This was disregarded. The weight rose to 240 pounds and sugar was again observed in 1941, when a doctor was consulted for pruritus vulvae. Subsequent weights were 211 and 180 pounds and in 1958, she came to me with a sore toe and showing glycosuria 2 8 per cent, blood sugar 237 mg , weight 172 pounds. With unusual pains I obtained the above history. Casual questioning would not have revealed it. Should we not date onset to the history of glycosuria in 1938? In case we do accept the onset from the transient glycosuria during pregnancy then the duration of diabetes in our cases would notably increase.

At birth in 1901, Case 31496, weighed 12 5 pounds Diabetes was recognized in the mother in 1927, after 26 years, and 17 years later it was discovered also, in the child who was so overweight when born Two younger sisters and a brother, through design on the part of the mother, had normal birth weights and have not as yet, 1958, developed diabetes

What splendid examples are the above of Marañon's ideas expressed many years ago regarding the long prodromal stage of diabetes before its actual recognition

Onset.—The date of onset of diabetes is usually indefinite in adults, whereas in children the diagnosis far more often can be assigned to a definite month, week or even day. The authors have zealously investigated this point, first with 500 cases, and subsequently Dr. White studied 1009 adults and 489 children In addition, the records were searched for cases with "sudden" onset (*i e.*, within twenty-four hours) in seven other groups of approximately 100 patients each and the percentage varied per group between 1 and 1 6 per cent, the average being 1 3 per cent.

The time of onset was considered "indefinite" if it could not be located within any two months' period, and 86 per cent of the adults fell into this indefinite classification, but only 35 per cent of the children. If the onset appeared to be within an interval of two months to one week it was considered "gradual," and this group claimed 9 4 per cent of the adults and 44 per cent of the children The onset was considered "rapid" if it appeared to occur during a period of six days, *in this group are 2 7 per cent* of the adults and 18 per cent of the children In fact, this percentage holds for 2191 children so studied An onset developing in the course of twenty-four hours was considered "sudden" and in this category are found 1.9 per cent of the adults and 3 per cent of the children, but we consider even these percentages far too high Over and over and over again a reported "sudden" onset will be found to be "gradual" or even "indefinite." (See page 93 for Boulin and for Pavel) Also Chapter 2, p. 32

The reason for statements in the literature that diabetes is of sudden onset may be due to imperfect histories, based more upon impressions or

Incidentally a remission of diabetes occurs in adults as well as in children Escudero seeks to determine the prodromal stage by slight alterations in

about the prodromal symptoms of diabetes. We should learn how to recognize its approach and not simply suspect it because of heredity and obesity

Irrespective of the type of onset, whether fulminating or slow, as soon as the diagnosis of diabetes is made the profession has come to regard the active stage of the disease, the progressive stage, completed and to feel that all the damage has been done This is contrary to common sense and analogy Even in hemiplegia the first few hours of the illness show rapid changes taking place about the embolus or the hemorrhage, which surgically or medically may be alleviated, and in an acute infectious disease there is no sharp line between pathological degeneration and regeneration During the beginning stage of diabetes the patient should be considered as in a labile condition and we should hold ourselves expectant to observe whether the disease is to become mild, moderate, or severe Quite likely it does not receive its stamp of severity at its very inception, but is severe or mild largely as the diet and the doctor decree If an established diabetes of moderate severity of long standing can be made to become severe by improper treatment, such as sudden restriction of carbohydrate and excessive administration of protein and fat, how much more easily may the diabetes in its nascent stage suffer increase in severity conversely what an opportunity exists for active prophylactic and therapeutic effort

Symptoms The recognition of the symptoms and signs varies with the intelligence of the patient and his social status and the time spent by doctors eliciting the same As a rule the approach of the disease, like that of the complication coma, is insidious Loss of strength polyuria polydipsia, and polyphagia are the commonest symptoms Polyuria is the most frequent symptom, being present in 73 per cent of the cases polydipsia in 67 per cent and loss of strength in 64 per cent stand next in importance Symptoms and signs referable to the skin existed in 31 per cent of the cases

Escudero Diabetes Aglucosurica Barcelona Manuel Marin 1930
Colwell Arch Int Med 70 523 1942
White Loc cit p 52
Berger Jour Am Med Assn 148 364, 1952

in early 1958. Sugar was found in April, 1958, with blood sugar of 212 mg He is comfortable January, 1959, with 35 units of NPH insulin.

These 100 patients with supposed onset above their seventieth birthday were found by examining the records of the last 4,075 diabetic patients coming for treatment, 1947–1951. This incidence in the eighth and ninth decade is 2.5 per cent, which is in contrast to 3 9 per cent incidence in the first decade. One hundred and fifty-seven children, incidence 3 9 per cent, were found in this same series. Thus, in the Joslin Clinic there was a greater incidence of diabetes in the first decade of life than in the eighth and ninth combined. Perhaps our clientele is overweighted with children.

Thus von Noorden and Isaac in the Eighth Edition of Die Zuckerkrankheit[21] gave a table summarizing the decade of onset of diabetes reported by six previous writers, and in this the percentage occurring in the first decade varies between 0 5 and 1.0 per cent, and in von Noorden's own series a percentage of 1.34 is recorded. Barach, in a compilation of 1100 cases finds 2.1 per cent in the first decade and 1 8 per cent in the eighth and ninth combined. At the Massachusetts General Hospital between 1824 and 1898, among the 172 diabetic admissions on the Medical Service, there were 3 or 1 8 per cent in the first decade and none above 70 years of age.

This high incidence of diabetes in the first decade in a series of diabetics does not imply an increased incidence for the total population, of which 21 7 per cent belong in the first decade and only 5 4 per cent from the eighth onward (See Tables 8, 9, 10.) Intricate statistical compilations by experts are necessary to form an idea as to the frequency of onset of diabetes or its true incidence in the later periods of life It will never be known until routine examinations of urine and blood are performed twice or more yearly.

The character of the diabetes of these 100 cases with onset at seventy years or above corresponds more to the middle-aged, fat, non-acidotic type than to the youthful, thin patient with liability to ketosis On the other hand, all types of diabetes are seen in this group, and by no means is it [illegible] cases, 9 of [illegible] Marked [illegible] ere made or lesions in the eyes found in 45, but in 55 there was definitely no such complaint The blood pressure was below 150 in 31, between 150 and 179 in 34, and 180 or above in 35 The weight in 16 cases was either standard or less than 15 pounds above standard. In 18 cases it was 15 to 29 pounds above, in 23, 30 to 49 pounds above, and in 15 cases 15 pounds or more overweight Glycosuria was under 1.0 per cent in 48 instances, but at the time many of these were under treatment All 5 patients with onset at eighty years or above were females, 3 married and 3 having borne children Of the total 61 females, 45 gave a history of pregnancy

The symptoms of the latent period, corresponding to the prodromal period in an infectious disease, in contrast to the symptoms of the clinical period at onset, are instructively discussed by Marañon [22] He emphasizes that this latent period should be utilized for preventive treatment, and how

[21] Von Noorden and Isaac Die Zuckerkrankheit, Berlin, J Springer, P 77, 1927
[22] Marañon Carrasco and Soler Arch d med cirugia y especialidades, 1924.

TABLE 36. DURATION OF LIFE SUBSEQUENT TO ONSET OF DIABETES AMONG 18,055 DECEASED DIABETIC PATIENTS IN EACH OF THE IMPORTANT ERAS OF TREATMENT

(Number and Per Cent of Cases Classified According to Duration)
(Experience of Joslin Clinic, 1897–1957*)‡

	Naunyn Era 1897–5/31/14		*Allen Era* 6/1/14–8/6/22		*Banting Era* 8/7/22–12/31/29		*Banting Era* 1/1/30–12/31/36	
Age Groups at Onset	*Number of Cases*	*Duration Years*	*Number of Cases*	*Duration Years*	*Number of Cases*	*Duration Years*	*Number of Cases*	*Duration Years*
All Ages	326	4.9†	836	6.1†	1,457	8.0†	2,681	10.3†
0–9	24	1.3	61	2.9	21	2.8	24	7.3
10–19	39	2.7	84	2.7	56	3.4	60	7.4
20–39	85	4.3	215	4.9	198	8.9	275	14.4
40–59	126	7.0	351	8.6	800	9.5	1,444	11.6
60 and over	51	4.4	117	6.4	379	5.5	858	7.0
Unknown	1	—	8	—	3	—	20	—

	Hagedorn Era 1/1/37 to 12/31/43		*Hagedorn Era* 1/1/44 to 12/31/49		*Charles H. Best Era* 1/1/50 to 12/31/55		*Charles H. Best Era* 1/1/56 to 12/11/57	
Age Groups at Onset	*Number of Cases*	*Duration Years*	*Number of Cases*	*Duration Years*	*Number of Cases*	*Duration Years*	*Number of Cases*	*Duration Years*
All Ages	3,623	12.1†	4,116	13.7†	4,376	15.6†	640	18.2†
0–9	36	10.3	58	18.5	107	20.6	30	26.4
10–19	79	11.4	125	16.2	198	20.1	52	23.5
20–39	399	16.9	464	18.8	621	21.8	91	25.1
40–59	1,911	13.4	2,214	11.9	2,284	18.2	304	18.7
60 and over	1,197	8.6	1,242	9.2	1,161	10.0	159	10.2
Unknown	1	—	13	—	5	—	4	—

*Deaths reported through December 11, 1957
†Based on cases with known duration
‡Prepared by Statistical Bureau of Metropolitan Life Insurance Company

Pruritus vulvæ is frequent and always demands exclusion of the diagnosis of diabetes Loss of weight is common, not always noted by patients, and

cipitating diabetes See page 69. Blurring of vision is not uncommon. Pain in the extremities was noted in 20 per cent. Polydipsia is a very important symptom. Often patients report that they have been water drinkers since early childhood. Polydipsia frequently precedes coma and not rarely is associated with a dilated stomach

Most of the symptoms which we involuntarily attribute to diabetes are really symptoms caused by complications and will be discussed under such heads Bouchardat recognized this a hundred years ago. The absence of complications in our Quarter Century Victory Medal diabetics is as gratifying as it is striking, but later on even they are not immune. (See page 236.) In contrast, complications are far more common than formerly, because now diabetics live so long that these have an opportunity to develop Thus neuritis, once thought by my colleagues and me to be exceptional in diabetics, proved to be very frequent when Dr. W. R. Jordan, who worked with us for two and one-half years, carefully examined patients with this in mind The same held true for gastric and duodenal ulcer and for cancer until the duration of diabetes trebled, thus prolonging the period of exposure

E. THE DURATION OF LIFE AND THE PROGNOSIS IN DIABETES

Between my beginning practice in 1897 and June 1, 1914, deaths among my diabetic patients numbered 326 and their known duration of diabetes was 4 9 years. In the subsequent eight years, largely as a result of restricted diets as advocated by Frederick M. Allen the duration of life of the 836 fatal cases rose to 6 1 years, children with onset in the first decade living more than twice as long, 2 9 years, instead of 1 3 years as in the earlier period Sombre as these results were they demonstrated that we were gaining on the disease and were not going through a Cyrano de Bergerac experience. Then came insulin and progress has leaped ahead. Now many diabetics are outliving their normal life expectancy, and in fact, on the aver-

rages for dia-
pproximately
all our cases

are traced up to 1953, and a large proportion of the remainder, since For example, all but 5 in the first 10,000 cases seen prior to 1932, have been followed up Only a few have been considered lost because neither the Metropolitan Life Insurance Company, a tracing agency, nor we ourselves considered them untraceable Thus, all but 23 of the 4219 children have been traced

The four tables, Tables 36, 37, 38 and 39 represent the senior author's contribution to the treatment of diabetes To trace, compile and record

Duration Years*	Hagedorn Era: 1/1/37 to 12/31/43 Number of Cases	Per Cent†	Hagedorn Era: 1/1/44 to 12/31/49 Number of Cases	Per Cent†	Charles H. Best Era: 1/1/50 to 12/31/55 Number of Cases	Per Cent†	Charles H. Best Era: 1/1/56 to 12/11/57 Number of Cases	Per Cent†
All Cases	3,623	100.0	4,116	100.0	4,376	100.0	640	100.0
Less than 5	611	16.9	553	13.5	464	10.6	57	9.0
Less than 1	77	2.1	69	1.7	73	1.7	10	1.6
1	106	2.9	104	2.5	76	1.7	12	1.9
2	119	3.3	110	2.7	84	1.9	6	.9
3	158	4.4	130	3.2	105	2.4	14	2.2
4	151	4.2	140	3.4	126	2.9	15	2.4
5-9	881	24.3	930	22.7	749	17.1	87	13.7
5	170	4.7	158	3.9	134	3.1	20	3.1
6	168	4.6	192	4.7	153	3.5	13	2.0
7	195	5.4	191	4.7	141	3.2	16	2.5
8	169	4.7	201	4.9	149	3.4	15	2.4
9	179	4.9	188	4.6	172	3.9	23	3.6
10-14	994	27.4	935	22.8	982	22.5	114	17.9
15-19	677	18.7	849	20.7	842	19.3	111	17.5
20 or more	459	12.7	836	20.4	1,334	30.5	267	42.0
Unknown	1	—	13	—	5	—	4	—
Average†	12.1		13.7		15.6		18.2	
Median†	11.5		13.0		15.0		17.8	

*Deaths reported through December 11, 1957
†Based on cases with known duration
‡Prepared by Statistical Bureau of Metropolitan Life Insurance Company

TABLE 37.—DURATION OF LIFE SUBSEQUENT TO ONSET OF DIABETES AMONG 18,055 DECEASED DIABETIC PATIENTS IN EACH OF THE IMPORTANT ERAS OF TREATMENT

(Number and Per Cent of Cases Classified According to Duration)
(Experience of the Joslin Clinic, 1897–1957*)

Duration Years†	*Naunyn Era* 1897 to 5/31/14		*Allen Era* 6/1/14 to 8/6/22		*Banting Era* 8/7/22 to 12/31/29		*Banting Era* 1/1/30 to 12/31/36	
	Number of cases	*Per cent†*	*Number of cases*	*Per cent†*	*Number of cases*	*Per cent†*	*Number of cases*	*Per cent†*
All Cases	326	100.0	836	100.0	1,457	100.0	2,681	100.0
Less than 5	217	66.8	463	55.9	592	40.7	636	23.9
Less than 1	63	19.4	72	8.7	74	5.1	110	4.1
1	51	15.7	108	13.0	131	9.0	111	4.2
2	53	16.3	121	14.6	125	8.6	115	4.3
3	23	7.1	97	11.7	128	8.8	151	5.8
4	27	8.3	65	7.9	134	9.2	149	5.5
5–9	58	17.8	210	25.4	401	27.6	819	30.8
5	18	5.5	49	5.9	99	6.8	155	5.8
6	10	3.1	51	6.2	86	5.9	166	6.2
7	9	2.8	46	5.6	86	5.9	172	6.5
8	16	4.9	36	4.3	71	4.9	160	6.0
9	5	1.5	28	3.4	59	4.1	166	6.2
10–14	32	9.8	89	10.7	246	16.9	616	23.1
15–19	12	3.7	40	4.8	145	10.0	349	13.1
20 or more	6	1.8	26	3.1	70	4.8	241	9.1
Unknown	1	—	8	—	3	—	20	—
Average†	4.9		6.1		8.0		10.3	
Median*	2.9		4.3		6.4		9.3	

TABLE 10 DEATH RATES PER 1,000 AND EXPECTATION OF LIFE AMONG DIABETICS COMPARED WITH GENERAL POPULATION* BY SEX AND AGE

(Patients Examined Between 1930–1951 in Experience Years 1947–1951 Experience of Joslin Clinic, Boston, Mass.)[1]

Age	Death Rates Per 1,000				Expectation of Life			
	Male		Female		Male		Female	
	Diabetics	Population	Diabetics	Population	Diabetics	Population	Diabetics	Population
10	2.6	0.6	2.6	0.4	43.6	59.0	45.0	64.3
15	4.6	1.1	4.6	0.5	39.3	54.2	40.7	59.4
20	8.0	1.6	8.0	0.7	35.4	49.5	36.8	54.6
25	13.1	1.7	13.1	0.9	32.1	44.9	33.6	49.8
30	15.2	1.8	15.2	1.2	29.3	40.3	30.9	45.0
35	12.5	2.5	12.6	1.6	26.3	35.7	28.0	40.3
40	12.1	3.9	12.3	2.4	22.8	31.2	24.6	35.6
45	17.5	6.4	14.6	3.7	19.3	26.9	21.2	31.1
50	24.1	10.1	19.0	5.6	16.1	22.8	17.7	26.7
55	35.0	15.9	29.4	8.5	13.1	19.1	14.6	22.6
60	55.8	23.8	43.7	13.4	10.6	15.8	11.9	18.6
65	73.4	34.5	56.5	20.6	8.8	12.8	9.6	15.0
70	92.7	50.3	79.8	34.1	7.1	10.1	7.4	11.7

Note: Excludes deaths within one week of first observation or hospital discharge. In the computations at ages under 45, the combined experience of both sexes was used.

*White persons, 1949–1951.

[1]Prepared by Statistical Bureau of Metropolitan Life Insurance Company.

data about 52,560 glycosurics of whom 43,000 are true diabetics, during 61 years of the practice of medicine, would have been an impossible task without the cooperation of the Metropolitan Life Insurance Company. Through its medical directors, and the most detailed help of its Statistical Department, under Dr. Louis I. Dublin, Second Vice-President, and more recently, Mr. Herbert H. Marks, Manager of Medical Statistics, and his associate, Mr. Mongelli, this enormous work was accomplished. The tables literally represent years of work by secretaries and assistants, and, above

TABLE 38.—THE CHANGING AVERAGE AGE AT DEATH AND AVERAGE DURATION OF DIABETES IN EACH OF THE IMPORTANT ERAS OF TREATMENT

(Experience of Joslin Clinic, 1897–1957*)

Era	*Number of Deaths*	*Average Age at Death, Years*	*Average Duration of Diabetes, Years*
Naunyn			
1897 to 5/31/14	326	41.5	4.9
Allen			
6/1/14 to 8/6/22	836	46.7	6.1
Banting			
8/7/22 to 12/31/25	538	51.3	7.5
1/1/26 to 12/31/29	919	60.0	8.4
1/1/30 to 12/31/36	2681	63.0	10.3
Hagedorn			
1/1/37 to 12/31/43	3623	65.1	12.1
1/1/44 to 12/31/49	4116	—	13.7
Charles H. Best			
1/1/50 to 12/31/55	4376	64.7	15.6
1/1/56 to 12/11/57	640	64.7	18.2

*Deaths reported through December 11, 1957

TABLE 39.—THE FOLLOWING TABLE, BASED ON FATAL CASES, SHOWS HOW MUCH LONGER CHILDREN, WITH ONSET OF DIABETES UNDER 10 YEARS OF AGE, ARE LIVING TODAY. ACTUALLY, ABOUT THREE-FOURTHS OF OUR 4,100 CHILDREN ARE STILL ALIVE

Years	*Number of Cases*	*Duration Years*
1897 to 5/31/14	21	1.3
6/1/14 to 8/6/22	61	2.9
8/7/22 to 12/31/29	21	2.8
1/1/30 to 12/31/36	24	7.3
1/1/37 to 12/31/43	36	10.3
1/1/44 to 12/31/49	58	18.5
1/1/50 to 12/31/55	107	20.6
1/1/56 to 12/11/57	30	26.4

all, by the help of my friends in the medical profession all over the world who were finally the source of the information received. Financial support in recent years has been received from the income of the Danish Insulin Fond of the *American Diabetes Association and this last year from the* Public Health Service.

The average duration of life for our deceased diabetics since onset of their disease has risen from 4.9 in the Naunyn era to 18.2 years in the Charles H. Best era, and the median duration from 2.9 to 17.8 years.

TABLE 41. MEAN AND MEDIAN DURATIONS OF DIABETES SUBSEQUENT TO ONSET AND OBSERVATION BY SEX AND AGE GROUPS AT ONSET AND OBSERVATION. PATIENTS EXAMINED IN THE NAUNYN ERA, 1897 TO MAY 31, 1914 AND TRACED TO DECEMBER 31, 1957.

Experience of Joslin Clinic, Boston, Mass.[1]

Age Periods	Both Sexes			Males			Females		
	Number of Cases	Mean	Median	Number of Cases	Mean	Median	Number of Cases	Mean	Median
ONSET									
All Ages	644	9.6*	6.9	374	9.9*	7.4	270	9.3*	6.1
Under 10	28	1.8	1.0	12	2.4	1.4	16	1.3	0.8
10–19	49	3.0	2.1	31	2.9	1.9	18	3.2	2.3
20–29	56	7.8	2.9	28	10.6	4.3	28	4.9	2.0
30–39	95	12.3	5.8	57	12.4	6.8	38	12.1	4.5
40–49	155	12.6	11.0	98	11.9	10.4	57	13.7	12.8
50–59	163	10.8	9.8	96	10.8	9.8	67	10.9	9.8
60–69	73	7.1	6.4	38	7.4	6.8	35	6.8	5.6
70 and Over	21	5.5	5.8	12	5.5	5.5	9	5.5	6.5
Unknown	4			2			2		
OBSERVATION									
All Ages	644	6.7	3.2	374	6.8	3.5	270	6.6	2.7
Under 10	26	1.3	0.8	12	1.9	1.0	14	0.8	0.6
10–19	47	1.9	1.4	28	2.0	1.1	19	1.8	1.8
20–29	49	4.6	0.9	25	6.2	2.1	24	2.8	0.7
30–39	78	9.9	2.8	44	10.8	3.7	34	8.7	2.0
40–49	127	9.1	5.5	83	8.5	1.7	44	10.3	9.5
50–59	159	8.4	6.7	94	7.7	6.6	65	9.4	6.8
60–69	126	4.6	2.9	72	4.9	3.0	54	4.2	2.7
70 and Over	32	3.9	3.0	16	3.4	2.0	16	4.1	4.3

*Based on Known Duration
[1]Prepared by Statistical Bureau of Metropolitan Life Insurance Company

Children with onset in the first decade of life whose duration I first recorded in days, later in weeks, still later in months, now live much longer, reaching 26.4 years for those who succumbed in 1956 and 1957. All decades of onset show gains so that even those with onset at 60 or more, who prior to 1914 lived 4.4 years now live 10.2 years. When all the living cases in each era have succumbed, one can expect the durations of survival to have advanced more Then one would know the true duration of diabetes for these respective epochs

Through the courtesy of the Metropolitan Life Insurance Company the duration of life of the total 644 cases seen in the first 1897–1914 period has been computed Of this number all but five are known to have died. The results are shown in two Tables 42 and 43. Based upon age at onset the duration is 9.6 years, but upon date of first observation 6.7 years. Data for both series, for the mean and for the median appear in Table 41. The true average duration has advanced from 4.9 years to 9.6 years.

The number of cases surviving a specified period of years of diabetes from dates of onset and observation is shown in Table 41. Space prevents detailed discussion, but it is clear that from 1897 to 1914 none with onset in the first decade survived 10 years and only 3 in 28 over 5 years. For onset at 70 years of age or over but 3 of 12 survived 10 or more years Based on dates of observation at first visit one in 26 of those first seen under 10 years of age survived 5 years and only one in 32 of those seen at 70 years or more survived 10 years.

So far as I know, no tables of this sort exist They show strikingly that the duration of life for diabetics can be considered to be far longer than we have usually considered it to be

Since the recent duration of life for diabetics dying in 1956 and 1957, reaches 18 2 years and more than half of our cases are living it is probable that eventually those seen in that period will survive an average of 25 years even if no new discoveries are made

In Tables 36 and 37 are shown duration of life subsequent to onset of diabetes among fatal cases in each of the important eras of treatment, the Naunyn, Allen, Banting, Hagedorn, and Charles H Best periods. In the earliest period [illegible]
66 8 per cent [illegible]
recent period [illegible]
the last few years is due to fatalities among admissions late in life The per centage of fatal cases who survived 20 years of diabetes in the Naunyn era (1898 1914) was 1 8 per cent of the total deaths, but of deaths in the Charles H Best era, between January 1, 1956, and December 11, 1957, they now aggregate 42 per cent

The average age at death of diabetics in the various epochs described is shown in Table 38 In the Naunyn era it was 44 5 years, rose twenty [illegible]

Therefore, any patient who dies under the age of 64 [illegible] years, or without having lived 18 2 years with his diabetes, lowers our standards The average age at death of diabetics is now so near that prevailing in the country

... fifty-five and about 2 to 3
tive figures for expectancy
ulation, male and female

In general today a diabetic has between ⅓ and ¾ the life expectancy of those about him. Even for ages 65 and 70, the expectation of life of diabetics has risen.

(a) CHILDREN.—See Tables 36, 37, 40, 41, 42, and 43. Of our 4219 children with onset under 15 years seen between 1897 and December 31,

TABLE 43.—NUMBER OF CASES SURVIVING SPECIFIED PERIOD OF YEARS FROM DIABETES FROM DATE OF FIRST OBSERVATION. BY SEX AND AGE GROUPS AT OBSERVATION. PATIENTS EXAMINED IN THE NAUNYN ERA, 1897 TO MAY 31, 1914 AND TRACED TO DEC. 31, 1957

Experience of Joslin Clinic, Boston, Mass.[1]

Age at Observation, Sex	Total	Survival (in years)			
		5 and over	10 and over	15 and over	20 and over
All Ages					
Both Sexes	644	255	157	89	52
Males	374	153	86	53	30
Females	270	102	71	36	22
Under 10					
Both Sexes	26	1	—	—	—
Males	12	1	—	—	—
Females	14	—	—	—	—
10–19					
Both Sexes	47	4	—	—	—
Males	28	4	—	—	—
Females	19	—	—	—	—
20–29					
Both Sexes	49	8	5	3	3
Males	25	6	3	2	2
Females	24	2	2	1	1
30–39					
Both Sexes	78	31	22	17	17
Males	44	19	13	11	11
Females	34	12	9	6	6
40–49					
Both Sexes	127	65	48	32	18
Males	83	39	27	19	10
Females	44	26	21	13	8
50–59					
Both Sexes	159	91	62	31	11
Males	94	53	32	16	4
Females	65	38	30	15	7
60–69					
Both Sexes	126	45	19	6	3
Males	72	26	11	5	3
Females	54	19	8	1	—
70 and over					
Both Sexes	32	10	1		
Males	16	5	—		
Females	16	5	1		—

[1] Prepared by Statistical Bureau of Metropolitan Life Insurance Company.

for all people, that one cannot expect the figures to change unless they live longer because of their greater medical supervision.

The expectations of life of our diabetics, with death rates per 1,000, at specified ages, as compared with the general population, have been computed by the Statistical Department of the Metropolitan Life Insurance Company on data available and are shown in Table 40.

For all ages the diabetic death rates are far greater, for males 3 to 8 times as great up to the age of fifty, and thereafter about twice as great;

TABLE 42.—NUMBER OF CASES SURVIVING SPECIFIED PERIOD OF YEARS WITH DIABETES FROM DATE OF ONSET. BY SEX AND AGE GROUPS AT ONSET. PATIENTS EXAMINED IN THE NAUNYN ERA, 1897 TO MAY 31, 1914 AND TRACED TO DEC. 31, 1957.

Experience of Joslin Clinic, Boston, Mass.[1]

Age at Onset, Sex		Survival (in years)			
All Ages	*Total*	*5 and over*	*10 and over*	*15 and over*	*20 and over*
Both Sexes	644*	381	237	140	77
Males	374	232	140	79	45
Females	270	149	97	61	32
Under 10					
Both Sexes	28	3	—	—	—
Males	12	2	—	—	—
Females	16	1	—	—	—
10–19					
Both Sexes	49	7	2	1	—
Males	31	5	1	—	—
Females	18	2	1	1	—
20–29					
Both Sexes	56	16	10	8	7
Males	28	10	7	5	5
Females	28	6	3	3	2
30–39					
Both Sexes	95	52	36	28	24
Males	57	34	22	17	14
Females	38	18	14	11	10
40–49					
Both Sexes	155	136	87	56	32
Males	98	72	52	30	18
Females	57	44	35	26	14
50–59					
Both Sexes	163	108	80	42	12
Males	96	75	47	24	7
Females	67	53	33	18	5
60–69					
Both Sexes	73	47	19	5	2
Males	38	27	9	3	1
Females	35	20	10	2	1
70 or over					
Both Sexes	21	12	3	—	—
Males	12	7	2	—	—
Females	9	5	1	—	—

*Includes 4 with age unknown—2 Males, 2 Females

[1]Prepared by Statistical Bureau of Metropolitan Life Insurance Company

are as encouraging as any with which I am familiar because they demonstrate that diabetics in middle life can on the average live more than 36 years.

(*d*) PHYSICIANS.—The incidence of diabetes mellitus among physicians is unknown. In the Arizona study 1 in 41 in that state and for comparison 1 in 36 in Rhode Island were identified. I consider these figures afford a better idea of the prevalence of diabetes among physicians than can be derived from the obituaries published in the Journal of the American Medical Association. I think one doctor in forty has diabetes. The number of diabetic medical students based on replies from 14 medical schools representing 3800 students was one in 271. Assuming this ratio to hold true for all medical schools there were 88 diabetics among 23,733 medical students in 1949. I suspect far more in 1958.

Death from diabetic coma among physicians has virtually disappeared. The last 2 cases were in 1931 and 1946. Now the chief problem is cardiovascular-renal disease from which between 1944 and 1948, deaths amounted to 83.1 per cent. Of these fatalities[25] coronary artery disease represented 55.9 per cent of all deaths, instead of 14.7 per cent of deaths before insulin. Fortunately, 90 per cent of all cardiovascular-renal deaths 1922 to 1948 occurred in physicians over age 55, and 71 per cent of these were in physicians who had passed the average age at death for all physicians (67.3 years) during 1948. The remaining 17 per cent of the 59 deaths in the years 1944 to 1948 were from: cancer 5, tuberculosis 1, accident 1, miscellaneous 2. It is notable that infection, gangrene and hypoglycemia caused no fatalities.

With such data at hand before a medical career is started, the young diabetic and the medical faculty of his choice before granting admission might agree (*a*) that he show none of the degenerative complications of diabetes, (*b*) that he demonstrate his ability and willingness to control his diabetes, (*c*) that his duration of diabetes at time of entrance be less than 15 years, and that (*d*) he has life insurance in force. Exceptions certainly will be made. If these minima are satisfied, it seems worthwhile for the diabetic to undertake the study of medicine and for the medical school to receive him. It is unlikely that the physician, once embarked on his course of medical study, will need to give it up if diabetes develops during his course.

(*e*) THE DIA[illegible]
treated at the [illegible]
and January 1, [illegible]
diabetes of the [illegible]
have died since [illegible]
living cases, who developed coma prior to January 1, 1940, is already 21.3 years. It seems now that the coma group ultimately as a whole would live more than 18 years (see page 376), the average for all our diabetics

[25] Bradley: Jour. Am. Med. Assn., 144, 441, 1950.

1957, there are approximately 3351 known to be alive, 817 dead, 22 untraced. Children who have lived over 40 years with diabetes number 8, 8 living, 0 dead; those over 35 years 75, 66 living, 9 dead; over 30 years 215, 176 living, 39 dead; over 25 years 689, 577 living, 112 dead, over 20 years 1214, 969 living, 215 dead.

TABLE 41 — EXPECTATION OF LIFE AT DIFFERENT PERIODS

Experience of the Joslin Clinic

Period	*Expectation of Life (Years)*	
	Age 65	*Age 70*
1948–1951	8 8 males 9 6 females	7.1 males 7 4 females
1939–1947	8 7	6 9
1929–1938	8 2	6 6
1926–1928	7 5	5 9
1922–1925	7 1	5 5

(*b*) EARLY INSULIN CASES —Our first 83 cases treated with insulin between August 7, 1922, and January 25, 1923, give a hint of prognosis of *diabetics in general. These 83 cases were selected because they were severe* diabetics and therefore one has a right to conclude that for diabetics *en masse* the prognosis would be somewhat more favorable Thus, of the original 83 patients, 63 have died at an average age of 48 3 years with a duration of the diabetes of 13 9 years. The remaining 20 cases in the group were alive in 1957, and the average duration of the diabetes in these 20 cases at that time was 37 years, making the average duration for all these patients thus far 19 5 years

The causes of death of 63 who died were

coronary thrombosis	15	diabetic coma	15
cerebral thrombosis	8	pulmonary tuberculosis	4
cardio-renal	4	pneumonia	3
renal	5	accident	2
cardiac	2		

gangrene, septicemia, erysipelas, cancer, and cirrhosis, 1 each

The above figures show that the true duration of life of all diabetics treated with insulin in 1922 is far more than shown by the 63 of the 83 who have died

(*c*) CASES WITH ONSET UNDER FORTY YEARS —In 1930 H C Shepardson,[77] now of San Francisco, studied the effects of diabetes upon the vascular system of 50 of our patients then under the age of forty years who had already survived the disease five or more years It has been possible to ... Twenty-

...ars and the

...hese cases

were cardiorenal 4, coronary 6, cerebral 3, renal 5, pulmonary tuberculosis

[77] Shepardson Arch Int Med , 45, 674, 1930

TABLE 45 – RATIO OF DIABETES PATIENTS REMAINING IN THE VETERANS ADMINISTRATION HOSPITAL SYSTEM* TO THE TOTAL VETERAN POPULATION BY AGE GROUP (1956)

Age Group	*Estimated number of living veterans in civil life, 12/31/56 (Thousands)*	*Remaining patients with diagnosis of diabetes mellitus Nov 30, 1956*			*Age-specific ratio of hospitalized diabetic patients to each 100,000 living veterans*		
		Total	*Prin*	*Assoc*	*Total*	*Prin*	*Assoc*
All ages	*22,699*[1]	*3,316*[2]	*820*	*2,496*	*14.7*[3]	*3.6*	*11.1*
Under 40	14,800	396	144	252	2.7	1.0	1.7
40-49	3,849	420	112	308	10.9	2.9	8.0
50-59	1,420	544	108	436	38.3	7.6	30.7
60 and over	2,530	1,956	456	1,500	77.3	18.0	59.3
Figures for Comparison All Ages Jan 31, 1951	1 18,930	2 2,330			3 12.3		

*Includes VA patients in VA hospitals, other *Federal hospitals* and VA contract hospitals. Prepared by the Department of Medicine and Surgery, Reports and Statistics Service, U.S. Veterans Administration, Washington, D.C., March, 1958

(*f*) Quarter Century Victory Medal Diabetics.—The purpose behind the Quarter Century Victory Medal for diabetics was to spread the idea that diabetics could live long and healthfully, to grant distinction to those who deserved it and to disclose what manner of life and treatment had made this possible. The medal was designed by Amelia Peabody in 1947 for The Diabetic Fund of the Boston Safe Deposit and Trust Company and is awarded upon recommendation of its Advisory Committee. To date eighty-two such medals have been distributed. The conditions upon *which the medal is granted are: (1) proof of diabetes of twenty-five years'* duration; (2) a healthy body as shown by routine physical examination with urine free from albumin; (3) eyes without diabetic complications such as hemorrhages, exudates and cataracts; and (4) arteries free from calcification as disclosed by *x*-rays of the chest, abdominal aorta (lateral view), pelvic arteries and those of the lower legs between ankle and knee.

The chief characteristic of the group is that the patients are symptomless, free from complications and leading happy lives. There are 26 males, 56 females, 58 are married, three divorced; offspring 88. The year of onset varied from 1913 to 1932, and age at onset 1.9 years to thirty-four years but there were only nine with onset after twenty-three years. At least 48, 62 per cent, had positive heredity. As a rule, the interval between onset and the beginning of insulin was short but there are exceptions and one did *not receive it until thirty-five years after the disease began. Only three* have died, two from cancer and one from glomerulonephritis. From their histories it is evident that their diabetes was aggressively attacked soon after its onset and for the next few years in nearly all of the group meticulously controlled with frequent tests of the urine and a diet low in carbohydrate and calories. These patients confirm the oft repeated remark of *Frederick M. Allen that diabetes is not necessarily progressive.*

(*g*) Diabetes Among War Veterans.—Through the courtesy of Dr. William S. Middleton, Chief Medical Director of Veterans Administration, I am able to present the status of diabetes among war veterans. The article was prepared by Mr. Daniel I. Rosen, now Director, Reports and Statistical Service, who compiled similar data for the ninth edition of this book. In a few places in the text I have interpolated figures appearing in the ninth edition to emphasize the magnitude of this diabetic problem.

In the United States in 1956, it is estimated there were roughly 14.5 million World War II veterans, 3 million veterans of World War I and earlier wars, and 4.7 million veterans of the Korean War, including about 0 million who also had service in World War II. The problem of diabetes among war veterans has three aspects, treatment outside of institutions financed by the veteran himself, by non-federal resources, and hospitaliza*tion in Veterans Administration hospital facilities.*

Although representing only a partial picture of the magnitude of the [illegible] treatment in Veterans Administration [illegible] of that portion of diabetes morbidity [illegible] to require hospital care. A review of current experience indicates that the magnitude of the diabetes problem among hospitalized veterans increases as the age of the veteran advances. *The latest figures, given in Table 45, show that on November 30, 1956,*

duration with gain rather than loss in tolerance, the retention of body weight, are good prognostic signs Carelessness and coma have ended the life of many a diabetic, and, of course, will continue to do so. Therefore, for careless cases cut the life expectancy one-third. Will the average diabetic live more or less years than have the average fatal cases for his age group thus far? (See Table 36) The chances are, so far as the diabetes is concerned, he will live longer. See Life Expectancy Tables 40 and 44.

Postpone a Prognosis.—Never hazard a prognosis upon the supposed severity of the diabetes at the first visit Cases often appear severe when first seen, but upon further acquaintance it is found that this is due to some temporary and alleviable circumstance, such as the presence of acidosis brought on by an infection, by the sudden institution of a fat-protein diet or simply lack of knowledge in the use of diet and insulin One cannot emphasize too strongly the mild character of most cases of diabetes. Therefore, we repeat the above in other words. Do not rest a prognosis upon the quantity of sugar in the urine, the percentage of sugar or fat in the blood, or even upon acidosis. These signs are transient.

The duration of diabetes is steadily mounting. For all our cases it has risen to 18 years but what I think of more importance is that compared with the period 1897–1914, when 1 8 per cent lived over 20 years, now over 42 per cent have lived over 20 years. At present we have 108 cases who have survived 40 years from the onset of glycosuria I have studied these carefully and frankly I cannot say that the proof of the diabetes was perfect before the 40-year period It is true that at the time we considered these patients diabetic, but tests were less accurate then and blood sugars less frequent, indeed, the Folin-Wu test for the analysis of blood glucose was published in the Journal of Biological Chemistry in 1919

The diabetic dies of his complications and not of his disease If he has diabetic coma and is under the age of twenty years, the chances are 99 per cent that he will recover If the patient is above the age of twenty years and has coma, the chances for recovery are 95 per cent If he has a carbuncle, instead of every [illegible]
recovery today are almos [illegible]
between January 1, 1946, [illegible]
per cen[illegible]
cent [illegible]
conser[illegible]
safely [illegible] approximates that of non-diabetics If the patient has pulmonary tuberculosis along with the diabetes, and even if there is a cavity, the chances for recovery are nearly as good as in non-diabetics no matter whether the patient is young or old. If he has symptoms of angina pectoris, his prognosis for duration of life has been less favorable than for the non-diabetic, although at least 3 cases survived their first symptoms by 10 years

F REMISSIONS, CURABILITY OF DIABETES AND CRITERIA FOR CURES

It is an error to speak of a cure of diabetes The use of the word survival is preferable just as it is in cancer (See page 94) The tendency to

there were 3,316 diabetic patients hospitalized in the Veterans Administration hospital system. Diabetes was the principal reason for hospitalization for 820 of these veterans and an associated condition for the remaining 2,496.

The effect of age on the long term trend can be measured by the prevalence rate of veterans hospitalized primarily for the treatment of diabetes per 100,000 living veterans population. The prevalence rate for veterans of World War I and prior wars on June 30, 1936, was 6 4 per 100,000 veterans, based on the fact that 284 patients were hospitalized with a principal diagnosis of diabetes. On November 30, 1956, the comparable number of veterans of World War I and prior wars hospitalized primarily for diabetes was 512, or 16.1 per 100,000 living veterans of these earlier wars. The increase in prevalence rates in the 20 year period was more than two-fold.

The hospitalized diabetes prevalence rates per 100,000 living veterans of World War II was 1 7 on January 31, 1950, and 1.8 on November 30, 1956.

Another index of the increased diabetes morbidity among veterans is the number of veterans discharged from the Veterans Administration hospital system annually. The number of veterans of World War I and earlier wars who were discharged after treatment for a principal diagnosis of diabetes increased from 6,539 in fiscal year 1949, to 11,536 in calendar year 1956. This is an increase of about 76 per cent. The younger World War II veterans' *corresponding experience reflects an increase of 83 per cent, from* 3,471 discharges treated for diabetes as a principal diagnosis in fiscal year 1949, to 6,360 in 1956

The table also reflects the relationship between veterans' age and the prevalence of diabetes which requires hospital care. The ratios pertaining *to hospitalized patients with a principal diagnosis are believed of particular* significance

The number of veterans receiving compensation for service connected disabilities or pensions for non-service disabilities on June 3, 1950, where the major disability was diabetes, was 11,892 and on September 30, 1956, was 15,818 Monthly value of payments in 1950 was $713,641 and in 1956, $1,096,851 World War II veterans in receipt of such payments numbered 7,130 (6,781 service-connected and 349 non-service-connected), World War I veterans of this category numbered 6,173 (169 service-connected and 6,004 non-service-connected), Korean veterans in this group numbered 2,245, all except one of which were service-connected, Regular Establishment numbered 270.

Prognosis.—The prognosis of diabetes depends first of all upon the general physical condition of the patient entirely apart from the existence

weight of the patient on the other, and fourth, upon your zeal, doctor, to provide for him the best treatment which modern medicine affords

The presence of obesity, a favorable heredity, an early diagnosis, followed by prompt treatment, the history of benign diabetes of several years'

months By this plan the individual can be classified as a proved diabetic of one or more months' duration The longer the duration of the proved diabetes, the greater the respect which will be attached to its cure Chance glycosurias and hyperglycemias resulting from errors in the laboratory, from operative procedures, from temporary infections, and abnormal diets preceding glucose tolerance tests, thus would be ruled out. Hyperthyroidism and hyperpituitarism would not be excluded and, therefore, a statement upon these conditions should be included in the report of the case.

(*c*) TEST FOR RECOVERY.—Glycosuria and hyperglycemia should be absent, while the patient is without diabetic medication, both before and an hour after a meal This meal must contain at least two-fifths of the carbohydrate for the day. The carbohydrate for the twenty-four hours should comprise at least two-thirds of the calories necessary to provide 30 calories per kilogram body weight Better still, the carbohydrate tolerance should be unimpaired as judged by a normal glycemic curve following the oral administration of 100 grams of glucose to the patient in the post-absorptive state.

(*d*) ESTABLISHMENT OF RECOVERY —A diagnostically proved case of diabetes of one or more months' duration, which conforms to the test for recovery at the beginning and end of an interval of five or more years, shall be considered cured

Medals.—Early in this century it became evident that certain patients did exceptionally well One of these was the president of an insurance company I was always impressed by the faithfulness with which he followed diet Then other patients of similar character in one way or another made an impression so that with the financial help of a patient we began the award of an "Expectation of Life Medal" and gave that to a

executed by Miss Amelia Peabody

With the advent of insulin, complications began to appear among our diabetics so that in the early 1940's, upwards of 85 per cent showed signs of degeneration in the eyes, the kidneys or the blood vessels, particularly of the heart Here again an occasional patient stood out without a sign of a flaw on physical examination This led us to create with the Advisory Committee of The Diabetic Fund of the Boston Safe Deposit and Trust Company a "Quarter Century Victory Diabetic Medal" to be awarded to that individual who after a quarter century showed nothing abnormal The criteria for it will be furnished upon request Up to now, some 82 of these Medals have been awarded A detailed report of these is given on page 230 It is true the criteria for such a medal are hard to devise and furthermore it has been pointed out that we do not give a medal for those who have gone through their diabetic career but have many "battle scars" for which often they are not directly responsible For these exceptional cases we feel that we should have a medal, just as one is cited for gallantry in war We are now having that under consideration Perhaps

diabetes is inborn and must remain so for life. In many it will never become manifest, in others only some exciting cause will disclose it, such as the

or even cure of the disease (see Ed. 7, page 336) later proved to be false, just as did a case described by Conn *et al.*[29] In this connection Rynearson has written a valuable paper upon hyperinsulinism among malingerers.[30]

Remissions[31 32 33 33a 33b,33c] of the disease are common when the exciting cause for onset is removed and prompt agressive treatment, soon after the onset of the diabetes is recognized, is instituted particularly in children, and this often drives it into hiding.

It is most dangerous to hint to a patient that he may be cured. One can speak of a remission because that implies the possibility of a relapse. As my son says, it is safer for the patient to prick himself daily and be reminded of his diabetes than to tell him to omit insulin, because then he may forget diet, body weight and exercise as well.

Remarkable remissions occur and such have been reported and in recent years more often as remissions than as cures. Lack of space forbids inclusion here. In general in these series the diabetes has come into the open because of obesity, an infection ("infection is nature's sugar-tolerance test"),[34] a diabetic glandular complication with subsidence after removal of the inciting cause, or it has been in an individual who early received prompt and energetic treatment. Even in the latter and most important group we have encountered no actual cure as measured by the standards we have set for ourselves. Today we would increase rather than reduce the severity of these criteria. Quite arbitrarily, therefore, the writers propose the following standards to which cures from diabetes should conform and by which they should be classified.

Criteria for Cures in Diabetes.—(*a*) DIAGNOSIS.—The diagnosis of diabetes shall be based upon a glycosuria of 0.5 per cent or more accompanied by a fasting blood sugar of at least 130 milligrams per cent or a venous blood sugar after a meal or on a glucose-tolerance test of at least 170 milligrams per cent on more than one occasion separated by an interval of at least one month.

(*b*) DURATION OF PROVED DIABETES.—The duration of proved diabetes, by repetition of the tests described under diagnosis, shall be recorded in

Med., 21, 487, 1946
477, 1947

257, 257, 1957

33, 1958
Childhood, 32, 193, 1957

126
p. 126

Chapter 9

THE TREATMENT OF DIABETES MELLITUS

By Elliott P. Joslin, M.D

Diagnosis Established.—Treatment Begun.—A diabetic comes to the doctor for relief of symptoms, polydipsia, polyuria, fatigue, loss of weight, disturbance of vision, pruritus, discomfort due to complications in the nerves, kidneys and blood vessels or troubles dependent upon some accom-

[illegible]

blood is employed In a glucose tolerance test at the end of two hours if normal the blood sugar will return to the fasting level

The diabetic immediately should learn by graphic methods what diabetes is and why it can be treated by diet, exercise, insulin or other medication Demonstrate to the patient by the scales the amount of sugar lost in the urine in 24 hours Case 15214, a girl 22 years of age in 1936, was so thirsty that she counted the thirty glasses of liquid she drank in 24 hours and went to her doctor the next day to find out why Her urine contained 7 per cent sugar, and the amount so lost in a day was over one pound This amount of sugar was weighed out and shown to her in a bottle, and then she was told first to compare it with amounts secreted on subsequent days, and second with the carbohydrate in the diet At once the total calorie value of the diet was reduced to 1500 calories, thirty calories per kilogram body weight [illegible]

(600 calo [illegible]

calories) [illegible]

this was raised to 20, 30, 40 units on successive days, and to 46 units on the tenth day when three blood sugar tests were normal—60, 120, and 120 mgs

it should be reserved for those who have lived 35 or 40 years with diabetes, even though they may show degenerative stigmata

At any rate, our Medals have encouraged us [illegible] to strive to give [illegible]

[illegible]

Hospital Teaching Clinic places emphasis on teaching rather than on nursing and only ambulatory patients are accepted. Costs are reduced to some extent and we hope they will be still lower. The management of the Hospital Teaching Clinic is under the direction of the New England Deaconess Hospital. Teaching is so effective that patients remain but half as long as formerly which of itself reduces costs, but we are striving for even more than this, so as to make it easy for the patient to return for a few days of education and review of his physical condition. We believe all large hospitals should discriminate in their admissions in the immediate future and not charge the patient who needs teaching, which often can be done for groups, the same amount as the one requiring hourly bedside care

Whenever possible, teach two or more patients together. This saves time and they help one another.

The Preliminary Diet.—A knowledge of the diet to be prescribed is a *sine qua non* of treatment, because this will be important as long as life lasts It can be easily summarized.

Carbohydrate.—A safe diet for the patient at the first visit should consist of a few staple foods, low in calories, due to restriction in fat, moderate in protein, with carbohydrate 100 to 150 grams, the latter being the value upon which most diabetics can live comfortably for life. Such a diet is as follows:

TABLE 46.—PRELIMINARY BASIC DIET

Bread, 1 slice at a meal
Orange, 1 at a meal
Milk, ½ glass at a meal
Egg, 1, or small amount of lean meat or fish at each of 3 meals
3 per cent carbohydrate vegetables, 4 large portions
Cereals, ½ portion
Butter, 1 ounce during the day
Crackers, 4 small ones

TABLE 47.—A BASIC 24-HOUR DIABETIC DIET READILY ADJUSTABLE FOR AGE, SEX WEIGHT APPROXIMATE VALUES CARBOHYDRATE 150, PROTEIN 72, FAT 68 GRAMS

Food	Portions	Ounces	Grams	Carbohydrate	Protein	Fat	Calories
Bread	3 slices	3	90	45	8	0	212
Orange	3 medium	15	450	45	0	0	180
3% Vegetables	4 portions	20	600	20	6	0	104
Cereal	½ saucer	½	15	10	2	0	48
Milk	1½ cup	12	360	18	12	12	228
Egg	1	2	60	0	6	6	78
Meat	5 oz	5	150	0	35	25	365
Butter	1 oz	1	30	0	0	25	225
Saltines	4		60	12	3	0	60
				150	72	68	1500

By no means is the diet in Table 47 suitable for all diabetics, but it is so simply composed that it can be adjusted up or down according to the sex, age, weight and activity Moreover, this diet can serve as a basic diet. The patient who learns and understands this diet can always refer back to it and change insulin and exercise to conform to what he originally found worked satisfactorily at the beginning of treatment and enabled him to keep the urine sugar free and blood sugar normal Often the change of only 15 grams of carbohydrate from one meal to another or to between meals will make the urine sugar free

Approximate values of carbohydrate, protein and fat in various foods in portions and per ounce and grams are shown in Table 48, as are their caloric value For convenience, these data are combined on a card easily carried in a pocketbook If a patient thoroughly understands these figures, he can make a shrewd guess as to the composition of most foods For detailed analyses of foods, see page 267, Table 52.

Twenty-two years later, in January, 1958, the above patient weighed 117 pounds, was aglycosuric and blood sugar 93 mgs. while taking 5 units of regular and 35 units of NPH insulin, while filling an important secretarial position. In all these twenty-two years, she has seldom lost a day's work

Such a graphic method is easily grasped and will not be forgotten. It is not the per cent of sugar in the urine at the given moment which counts, but the total quantity lost in 24 hours which does the harm and makes the symptoms—the loss of strength and weight, thirst, frequent urination and local irritation. Having established these points about diabetes in the patient's mind, then it is logical for him to wish to learn how to correct them (Today, in a week rather than in three weeks one would inaugurate the treatment and train the patient, but it is questionable whether in a case of such severity that is desirable. Milder cases require less time to control, but do we educate these hopeful patients sufficiently? One is proud to treat without any interruption of the day's work, and this is often desirable, but here too education must not be neglected. A cooperative wife under such circumstances is most helpful)

In clinical computations, due to the great variations in the composition [illegible]

[illegible] sugar lost in the urine, one would never record fractions of a gram unless an exact metabolic experiment was in progress

Before prescribing a diet for a new or old patient it is desirable to know what the patient has been eating Time will be saved by asking specific questions rather than allow the often forgetful patient haltingly to describe it Thus, ask (1) Do you eat 1, 2, or 3 slices of bread at each meal, remembering most of the carbohydrate will always be in the form of bread, and that 1 slice of bread, if weight 1 ounce or 30 grams, contains one-half carbohydrate or about 15 grams (2) Do you have fruit one, two, three or more times daily?—assuming a medium orange contains about 15 grams (3) Do you have cereal for breakfast?—a large bowlful of oatmeal or one-fourth less of other cereals by weight or a package of dry cereal contains about 20 grams carbohydrate (4) Do you take potato for lunch and dinner? —one moderate portion is about equal to 1 slice bread, 15 grams carbohydrate (5) How many portions of 3 and 6 per cent vegetables do you eat?— [illegible] 20 grams carbohydrate (6) [illegible]

butter, oil, pastry, candy and sweet drinks? If one can get an idea of the quantities consumed of the foregoing articles one can make a shrewd estimate of the carbohydrate and total food eaten and thus can avoid drastic changes in diet for the first 24 hours

of sugar in the urine When the grams of sugar-forming material which he eats are transformed into similar amounts of sugar in a container and com-

e g , 5 quarts or 5000 cc. × 0 1% = 5. grams, or about the weight of a Buffalo nickel, and how little is needed to raise the blood sugar in a reaction if taken in the earliest stages. In Table 49, the diets for normal and diabetic individuals are compared

TABLE 49 —DIETS COMPARED IN GRAMS AND CALORIES FOR NORMAL AND DIABETIC ADULTS

Weight 132 lbs (60 kgs) Office Work

Food	Normal Grams Calories	Diabetic Grams Calories
Carbohydrate	250 × 4 = 1000	200 × 4 = 800
Protein	75 × 4 = 300	80 × 4 = 320
Fat	60 × 9 = 540	80 × 9 = 720
	1840	1840

1840 ÷ 60 = 31 calories per kg 1840 ÷ 60 = 31 calories per kg

In general a diet should be prescribed so that it can be increased rather

tests in the office

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family, including the etiology in the particular case At the same time it affords an opportunity to emphasize prophylaxis against diabetes among the relatives A complete history and physical examination are fundamental The patient will thus gain confidence and hope, and the doctor a knowledge of the disease which will establish a background and constantly be referred to as long as life lasts. Only when the physician realizes that

TABLE 48.—A POCKET DIETETIC CARD

Water, clear broths, coffee and tea, can be taken without allowance for food content

30 Grams 1 oz. Contain Approximately	*Carb C. Gram*	*Protein P. Gram*	*Fat F. Gram*	*Calories*
Bread, 1 large slice	15	2.5	0	70
Oatmeal, large portion	20	5	2	118
Crackers	20	3	2	110
Vegetables, 3% + 6% 4 large portions	20	6	0	104
Potato	6	1	0	28
Milk	1.5	1	1	19
Egg, 1	0	6	6	78
Meat, lean	0	7	5	73
Chicken, lean	0	8	3	59
Fish, fat-free	0	6	0	24
Cheese	0	8	10	122
Bacon	0	5	15	155
Cream, 20% light	1	1	6	62
Cream, 40% heavy	1	1	12	116
Butter	0	0	25	225

VEGETABLES, fresh or canned

Reckon average carbohydrate, utilized, 3%; 6%, 20%

3 per cent	
Lettuce	Tomatoes
Cucumbers, raw	Radishes
Spinach	Water Cress
Asparagus	Snap Beans
Celery	Cauliflower
Mushrooms	Cabbage
Rhubarb	Egg Plant
Sauerkraut	Broccoli
Endive, raw	Green Peppers
Swiss Chard	Kohl Rabi
Beet Greens	Kale
Dandelions	Summer Squash

6 per cent	*20 per cent*
Turnip	Potatoes
Carrots	Shell Beans
Okra	Baked Beans
Pumpkin	Lima Beans
Onions	Corn
Squash	Boiled Rice
Brussels Sprouts	Boiled Macaroni
Beets	
Green Peas	

FRUITS, fresh or canned (water packed)

Food	*Carb 10*	*Grams 15*
Grapefruit Pulp	150	225
Strawberries	150	225
Watermelon	150	225
Cantaloupe	150	225
Blackberries	120	180
Orange Pulp	100	150
Pears	90	135
Peaches	90	135
Apricots	80	120
Raspberries	80	120
Plums	80	120
Pineapple	70	105
Apple	70	105
Honeydew Melon	70	105
Blueberries	70	105
Cherries	60	90
Banana	50	75
Prunes (cooked)	50	75

1 gm. carbohydrate, 4 calories
1 gm protein, 4 calories
1 gm fat, 9 calories
1 kilogram (kg) = 2.2 lbs
30 grams (g) or cubic centimeters (cc) = 1 oz. A patient "at rest" requires 25 calories per kg.

Without a knowledge of arithmetic, including the metric system, it is extremely difficult for the patient to understand and control his disease with diet and insulin, but it can be done even if the patient cannot read or write. He must realize the amount of glucose-forming material in his food and note whether a change in it during treatment will lower the output

SYMPTOMS AT SINCE ONSET

	Wgt	Hgt	Date
Usual			
Maxim			
Onset			
Present			

a) Wgt loss
b) Polyuria
c) Polydipsia
d) Polyphag
e) Strength loss
f) Pruritus
g) Mouth dry
h) Leg cramps
i) Leg pains
j) Int. claud
k) Reaction
l) Coma
m) Vision

SYSTEM REVIEW a) Eyes
b) C R Pain
Cgh Dysp
Sput Orth
Hemop Palp
Ed

c) E-N-T
d) G I Bowels
App Lax
N [illegible] Mel [illegible]
Pain
e) Menses

f) G U Hes
Dys Dr
Freq Incont
Noct
g) N M
h) Allergy
penicillin
sulfa drugs
others

LAST CHEST X-RAY
LAST E K G

TREATMENT TO DATE
Insulin begun units how units
Diet begun present (see below) C P F
Urine tests how often results
Oral treatment begun
Variety

PRESENT ILLNESS (Chief Complaint)

HISTORY SHEET USED FOR INITIAL GUIDE TO TREATMENT AT THE JOSLIN CLINIC

Name
(Spouse) Age Ref by Dr
Address Race Add Clinic No
Born Yr
Occ Pt Hus Par Mo Fam Dr Date
Birthplace Add
Pt. Phone
FAMILY HISTORY F d 1 age M d 1 age
Bro d ages Sist d ages Children ages B wt
1 ages 1 ages Twins
HABITS C_2H_5OH Tob ic Spouse d. 1 D M. + O
PAST HISTORY S F Pneu Phys Act D M spouse's family
Herpes Z P A Epilep Gout V D Kid R F Jaund Other diab rel
Tons Diph Meas Mumps Pert.
H B P Other
SURG AND/OR HOSP ADMISSIONS Since
ONSET Date
Age Sudden (24 H) Grad (to 2 mo) Cause of exam
Sugar first discovered Rapid (1 wk) Indef (2 mo +) SYMPT
Last prior exam
Insurance
ETIOLOGY a) HEREDITY 1 Hereditary 2 Familial 3 Add'l Heredity Routine
b) Obesity c) Dietary excess d) Trauma e) Other
Date

	HOME DIET					Estimated		
	Weighed DATE							
Food	Breakfast	Dinner	Supper	Bedtime	Total Grams	Carbohydrate	Prot	Fat
Bread								
Cereal								
Fruit								
Veg. 3% & 6%								
Crackers								
20% Veg								
Milk								
Cream 20%								
Eggs								
Meat								
Fish								
Bacon								
Butter								
Pastry								
Insulin								
					TOTAL			
	MULTIPLY FOR CALORIES					×4	×4	×9
	TOTAL CALORIES =							

Blood Sugar

Urine Sugar

DIAGNOSTIC IMPRESSIONS

TREATMENT & DISPOSITION

For Follow-up Relative or Friend

Name

Address

PHYSICAL EXAMINATION

APPEARANCE Alert Yes / No — Hair — Skin & MM — TONGUE: TEETH

EYES Pup — Vision — BREATH Acetone — Kuss — GUMS. TONSILS:

HEARING — NODES C SC — A I E

Pulse — ARTERIES 0 1 2 3 4 — BL PR R L — THYROID.

HEART NSR / other — Apex Size — Sounds — BREASTS.

LUNGS R — L.

ABDOMEN — Liver — Spleen — Kidneys — Hernia

RECTUM — PELVIC: PROSTATE:

NEUROLOGICAL
Knee Jerks
Ankle Jerks
Babinski
Vibratory
Sensory
Motor

JOINTS

EXTREMITIES		
Edema	R.	L.
Dors Pedis	R.	L.
Post Tib	R.	L.
Popliteal	R	L.
Femoral	R	L.
Epidermoph	R.	L.
Insulin Hyper	R.	L.
Insulin Atrophy	R	L.

FUNDI:
R.

L.

HOME DIET		Weighed DATE			Estimated			
Food	*Breakfast*	*Dinner*	*Supper*	*Bedtime*	*Total Grams*	*Carbohydrate*	*Prot*	*Fat*
Bread								
Cereal								
Fruit								
Veg 3% & 6%								
Crackers								
20% Veg								
Milk								
Cream 20%								
Eggs								
Meat								
Fish								
Bacon								
Butter								
Pastry								
Insulin								
					TOTAL			
	MULTIPLY FOR CALORIES					×4	×4	×9
	TOTAL CALORIES=							

Blood Sugar

Urine Sugar

DIAGNOSTIC IMPRESSIONS:

TREATMENT & DISPOSITION

For Follow-up Relative or Friend

Name

Address

much in the first interview by talking with the patient that I always begrudge allowing the history to be taken by an assistant, because he may see the patient temporarily, whereas I hope to follow the case throughout his or my life. *During the process a great deal of information can be given,* errors detected, doubts removed, and reasons for treatment explained. The sheet we have found useful as an initial guide to treatment and especially

adapt the diet to their gain in tolerance As a rule the evening meal should be the heaviest in the day and especially rich in protein.

Diets.—Diets are better utilized if spread out through the twenty-four hours. In preventing reactions a few grams of carbohydrate given at the first symptoms are worth more than many times the quantity when the reaction is well established. Taking advantage of these two features, patients exposed to and most annoyed by reactions are often given a little *carbohydrate every hour on the hour between meals until they gain con-*fidence and learn how the diet, insulin and exercise are interacting. By a device of this sort the group of so-called "brittle" diabetics melts away.

Today the patient should become sugar free promptly and more rapidly than described at the beginning of this same chapter 22 years ago It is a general rule in diabetic coma to plan for a diabetic when hospitalized, to become free from glycosuria and acetonuria within 24 to 48 hours Why should not the same rule appl

and less lacking in control?

patient returns to the office

hospitalized, because of the attendant expense Insulin is so wonderful *that one wishes the patient to experience the value of it immediately.*

First Dose of Insulin.—(See also page 282 for use of insulin and page 301 for treatment with oral drugs. For insulin in surgery see page 595, in pregnancy, page 706, in diabetic coma 362.)

The amount of the first dose of insulin is immaterial provided it is so small that by no chance a reaction will follow It can be repeated and increased every six hours if indicated Seldom would one begin with more than 8 units which the patient

is so close that aglycosuria can

practical only when patient ar

would feel safe to give 8 units of regular insulin to decrease nocturia the *first night, and 8 units of NPH* insulin to clear up the urinary sugar in the early morning hours by the first urination Most diabetic patients taking insulin will stay controlled with 20 to 30 units daily The few patients

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Their

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disease and in their symptoms in the first twenty-four hours is always striking, and this is always aided if other diabetics are present who will confirm what the doctor or nurse may have said If a child, or adult who has survived diabetes 35 years, is in the office and introduced to the new comer, I don't worry about the impression I have left upon that patient or his family

Maintain Daily Routine.—The regular routine of life need not be changed if one is dealing with a trustworthy patient Dr George R Minot, case number 2383, my most noted case of diabetes because of his part in the discovery of the liver treatment of pernicious anemia, showed 7 1 per cent sugar on October 15, 1921, readjusted his diet for his evening meal that same afternoon, attended to his hospital duties at the Massachusetts General Hospital the next morning, and became sugar free on October 18, 1921, *even though at that time insulin was not available* A large amount of sugar by no means is a deterrent to such a course of treatment I was

More time for sleep, relaxation and exercise is desirable for diabetics than for normals and so they require fewer calories For growth they need as much, but never more than the normal and whether young or old they must always guard against overnutrition Doctors of diabetics always should know what they themselves eat, otherwise their understanding of what to prescribe for a diabetic is apt to be faulty Unless a doctor or a nurse does know the approximate carbohydrate, protein and fat with total calories in his own diet, I don't want to trust him or her with the care of my patients Indeed, I have made a rule to record my signature in a gift of this monograph to an assistant only when the values of foods which he has weighed and eaten during 24 hours are recorded on the front page Most doctors in my experience think they eat at least 500 calories more than their actual total, and only recently a doctor reported eating 3300 calories when I could see from his dietary calculations that he was actually consuming about 1000 less

Don't overwhelm the patient with knowledge at the first visit There is so much for the diabetic neophyte to learn that one must use judgment as to how much should be taught at the beginning Otherwise, he will be overwhelmed with new knowledge about the disease and the complexities of its treatment As a rule, however, in the first two visits the patient can learn the fundamentals of the diet and how, by changes in it, he is being

made sugar free. He should learn whether he is over- or underweight and [illegible]

[illegible]

realize something active has been done for his comfort and salvation.

Aggressive Treatment.—Naunyn clinically recognized that the case apparently severe if aggressively treated often would surprise one by becoming mild, whereas the mild case neglected invariably would become severe. How true his conception of treatment was has been proved by the lengthening lives of patients who followed his advice and the early deaths of those who failed to heed it. Reasons for this belief both experimental and clinical, though Naunyn was not mentioned, were brought out in an article by Brush in 1944.[1] Naunyn, Cantani, Bouchardat, Allen and Boulin[14] also believed in rest for the pancreas.

In his paper on the "Initial Stabilization of the Diabetic Child," Brush pointed out that children who had had no previous treatment for diabetes, *regardless of the severity of symptoms, are capable of recovering an appreciable capacity to regulate the blood sugar provided enough insulin is given to relieve the islands of Langerhans of any need for its production.* The pancreas is rested. The regimen is applicable to children of all ages I will add that older patients respond to it quite as readily.

Exercise is kept at a uniform level and the diet prescribed is calculated for the patient's age and weight so that the only variable is the insulin. At first this is administered in liberal amounts, by his plan 2/3 as many units as the grams of fat in the diet, and is kept constant at a relatively high level even though the patient has moderately severe shocks which mark the initiation of the period of functional recovery of the islands. *From this point on, the rate of recovery, as measured by the decrease in requirement for insulin is so uniform as to be usually predictable.* After hospitalization for 22 to 30 days the child can be discharged, free from glycosuria, essentially free from shock and in a stable state on a full maintenance diet controlled by a single daily injection of insulin of between 2 and 8 units Brush gave 4 or 5 units of regular insulin about 4 A.M., 4/7ths of the remaining dose before breakfast, 1/7th. before the noon and 2/7th before the evening meal With 21 of his 30 cases, good results were obtained in 30 days In another group of 7 cases, the duration of treatment was prolonged, but finally control of the diabetes was attained Five cases with infections did not react as well. The frequency of insulin shocks heralded the phase of recovery He writes—"The golden opportunity for bringing about maximal functional recovery may present itself but once." [illegible] The point is to [illegible] did [illegible] ble

course of many of our Quarter Century Victory Medal cases

[1] Brush Loc cit p 216
[14] Boulin Semaine Hôp de Paris, *34*, 2024, 1958

Resting the Pancreas.—This idea of resting the pancreas really goes back to Naunyn's observation already cited Bouchardat and Cantani also recognized the necessity for early, strict treatment over prolonged periods Such a plan of treatment is supported experimentally with animals by

normal occurred Lukens and Dohan[4] succeeded in producing permanent diabetes in cats by removing one-half to three-quarters of the pancreas and

and goading action of hyperglycemia will result in a certain amount of recovery of islet cells provided there is an allowance period for restoration of the damage done In Houssay's laboratory the same principle was shown by his associate Foglia with his 95 per cent depancreatized rats[5]

It is unfortunate that the later course of this Brush series of cases is not known. Since the introduction of insulin I have noted these periods of

examples of a remission in diabetes To these I will add another because in this patient it was shown by Doctors Renold and Martin that the blood sugar lowering component of the blood (insulin?) was tested and found even above normal eight weeks after recovery from diabetic coma with a glycosuria and glycemia treated with 1600 units

The following cases represent examples of remissions which have come under my observation years ago Unfortunately, as in the Brush series,

if one seeks for them in adults fully as striking instances are seen and some

[2] Allen Jour Metab Research, *1*, 5, 1922
[3] Best, Campbell and Haist Jour Physiol , *97*, 200 1939

of them have been followed for years and now are in such good condition one is tempted to consider the possibility of a cure of the disease or to doubt the accuracy of the original observation

REMISSION OF DIABETES CASE 6095.—A boy, 5 years old in November, 1926,

normal as shown below:

	Urine	Blood
Fasting	Negative	60 mg per 100 cc
1st hour		113 mg per 100 cc
2nd hour		111 mg per 100 cc
3rd hour		50 mg per 100 cc.

merulo-sclerosis and retinopathy in 1951

ie fol-
8 mg

The next three cases show the slow onset of the disease in children

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when first seen
The glycosuria
2, all specimens

insurance company

The major factors which favor remission are rest to the pancreas, brought about by relieving it of the need for manufacturing insulin, by an adequate

disease and his thesis for its treatment

Naunyn also thought, as do we, that diabetes is hereditary and that heredity is the red thread which is present in all its forms and proves the unity of the disease Thus a grandparent and a grandchild both show diabetes and so do several of their relatives It is unreasonable to conclude that two distinct types of a disease have attacked the same family Reflect upon the severe and mild manifestations of the disease in the same patient,

Case 8095, page 256, with varying amounts of insulin-lowering material in the Islands Incidentally, heredity shows where we should look for new cases of the disease, namely, in the *families of diabetics*. *No diabetic or relative of a diabetic should ever be fat.* Recalling Marañon's as well as Naunyn's ideas, efforts for the prophylaxis of diabetes should concentrate upon the prevention of its greatest precursors, overgrowth and obesity, in everybody and especially in all those with a hereditary tendency to it. I admire Naunyn* so much and my several visits to him were so helpful that below I give excerpts from his monograph which have exerted so great an influence on my treatment of the disease during the last sixty years.

"Although the course of the disease is by no means exclusively dependent upon glycosuria, yet it is the *important symptom, because in general its* [illegible]

patient, earlier or later, always serious danger through exhaustion and dangerous complications."

[illegible]

the tolerance"

"Each severe glycosuria in a diabetic ought permanently to be prevented since it will sooner or later become threatening, indeed the glycosuria ought to be banished on account of the favorable influence which the aglycosuric condition exerts on the tolerance Unconditionally, this must be attempted at the beginning of treatment"

"Above all it is important for the first traces of the diabetes to be energetically treated at their first appearance in order that, if possible, the conquest of the glycosuria may be obtained I consider it in my experience very probable that among the early, strenuously treated cases, which in the beginning imposed themselves as being very severe but later on ran a [illegible] early, strict treat- [illegible] no doubt that the [illegible] ergetically treated, [illegible]

[illegible] on the doctor [illegible] of the doctor is and remains to maintain the patient for a long time in a bearable condition of life' According to my view the treatment has a broader and more definite purpose, namely this. to better the disturbed function or at least to prevent its further deterioration, the progressive development of the disease It is understood on the other hand that it is allowed transitorily to undernourish the patient provided thereby it is only in this way possible *to obtain control of the disease*"

Cantani recognized the advantages of rigorous control of the disease To accomplish it he would provide the patient with a private room if necessary, with a lock on the door to guard against diabetic errors which, since Rollo's

* Naunyn *Diabetes Mellitus, 2nd ed. Wein, Alfred Holder, pp 310-392, 1906*

time and his patient Captain Meredith, have so often confused the interpretation of treatment. Naunyn appreciated Cantani's contribution.

Historically, it is also important and a just recognition of the greatest diabetic clinician the world has ever known to summarize Bouchardat's attitude toward the disease a hundred years ago.[10]

Bouchardat's[11] life and soul were wrapped up in the problems of diabetes [illegible]

[illegible] balancing the handicap of the disease. Above all else, Bouchardat was the apostle of hope in a diabetic world of despair.

[illegible]

became free from diabetes for ten years until at the age of eighty it reappeared, thus illustrating the insidious onset and sly return of the malady.

Even before Marañon, Bouchardat appreciated the latent stage of diabetes. He cites the following—"M. Marchal (de Calvi) partage mon opinion sur ce sujet, et d'une manière encore plus exclusive." "L'époque, dit-il (1) de la Manifestation du diabète n'est pas du tout celle de sa production, et la maladie existe souvent pendant très longtemps sans donner lieu à des symptômes characteristiques, symptômes qui peuvent, un jour, éclater tout à coup . . ."

Although Bouchardat devised all sorts of measures to make the forbidding, nauseating, rancid meat-fat diet of Rollo palatable, he never lost sight of the fact that the aim of treatment was to keep the urine sugar free. Primarily he lowered the carbohydrate in the diet by his limitation of bread and the exclusion of milk. He introduced the use of gluten bread, but he had no illusions regarding it. He did not want to be called a "gluten bread doctor." He advocated moderation in its use as well as of all foods in treatment. "*Mangez le moins possible*." He noted the favorable effect of undernutrition during the Siege of Paris. He occasionally fasted a patient. He emphasized green vegetables and even washed them to lower the carbohydrate.

Bouchardat was the first to utilize exercise to control the glycosuria. He pushed this to the limit in season and out of season. He explained in many ways to his patients the good effect of exercise, and in support of it he cited the high incidence of diabetes among the professional classes in contrast to that among manual workers.

[10] Bouchardat. De la Glycosurie ou Diabète Sucré, Paris, Baillière, 1875.
[11] Joslin. Diabetes, *I*, 100, 1952.

He recognized that the mental capacity of the patients was retained long after the loss of muscular and nervous power, though he admits that the memories of his patients suffered. He observed the diminution and occasional regain of sexual activity both in males and females, although he stated in his first edition in 1875 and again in the second in 1883: "*1. Les femmes atteintes de vrai diabète sucré deviennent très-rarement enceintes. 2. Dans le nombre si considérable de diabétiques qui sont venus me consulter, je n'ai pas mémoire d'avoir vu une seule femme enceinte.*"

Bouchardat suspected the pancreas as the cause of diabetes. He was the first to attempt to prove this by its removal, but surgery then was too crude. Bouchardat was a good chemist. He noted the difference in

and urine of his patients with severe diabetes, but did not clearly associate it with diabetic coma although recognizing coma could be precipitated in such cases and for them he prescribed relaxation. He determined the intake and excretion of carbon dioxide and pointed out the advantages of potassium in the low carbohydrate vegetables.

Although he knew alcohol was not directly sugar producing, more and more as he grew older he restricted its use.

Bouchardat examined the blood for sugar, even though to carry out the test it required 300 cubic centimeters. He explained why it was that glycosuria could be high and glycemia low, because in one the percentage found in the urine represented the quantity secreted by the kidney during an average period of several hours but with the other it was the analysis of the existing sugar in the blood for the moment. In emphasizing the frequency and ready detection of diabetes he related how even a hotel bell-boy had diagnosed the disease in an old man by observing the white spots on his pants which would not brush off or disappear with benzine, but would wash off with water.

Bouchardat wrote simply and clearly. His French is therefore easy to read. I wish that space permitted quoting some of the sentences which constantly are in my mind. It is most unfortunate that his monograph was not translated immediately into English, because thereby in this country we failed to benefit from it for almost two generations.

Apollinaire Bouchardat was born in 1806 and died in 1886. He was buried in Paris in Père LaChaise cemetery. *Would that his spirit might* know the gratitude of diabetics whose lives he prolonged and made endurable and to whom he gave, and still gives, courage and hope.*

Details Concerning Calories.—For a quarter of a century I treated diabetics with only diet and exercise. During this period there was a steady lengthening of life and a reduction of deaths from diabetic coma, from 64

to 40 per cent. In the following pages I have copied from earlier editions those details about calories, diets and specific foods which I found most helpful

Composition of Normal Diet and Calories Consumed.—Eighty per cent of the population today lead an urban life and with the advent of machinery

but we believe is seldom less than carbohydrate 150 grams, protein 60 grams, fat 60 grams, or more than carbohydrate 350, protein 125, fat 120 grams, respectively.

My own metabolism, a non-diabetic, was studied carefully on various occasions and the results made a strong impression upon me that less food

This was minus 8.9 per cent compared with the predicted 1498 calories, 24 per kilogram At that time I certainly thought I was as active as any physician At age seventy-two, weight 59 kg and height 175 cm, the metabolism was repeated and coincidentally with advancing age it fell, so that on February 19, 1941, the results were 1207 calories per twenty-four hours, or minus 5 per cent, compared with the predicted 1268 calories. At age 87 the total calories in the day were about 30 per kg Carbohydrates 194, protein 61, fat 83 g

active children on my farm The results are shown in Table 50 For very young children calories per kilogram rise to 70, 80, 90 or even 100 per kilogram in infancy or the first two years of life and likewise for under-nourished children and those with retarded development *Benedict*[12] *is*

hours She was confined to her bed with hemiplegia for a year, remained sugar-free, and held her weight Her diet was accurately weighed by a trained nurse for the entire period

Variations in Caloric Requirements in Daily Life.—The caloric needs of the body

to momer

weight pe

rest in a horizontal position and 1 2 calories while sitting in a chair In other words, 20 per cent more energy is required to sit in a chair than to lie on a couch At the Nutrition Laboratory normal men at rest eliminated

[12] Benedict New England Jour Med, 212, 1111, 1935

TABLE 50.—DIET OF HEALTHY CHILDREN

Age	Subject	Weight		Height		Carbo-hydrate	Protein Grams	Fat	Calories		
		Kg.	Lb	Cm	Inches				Total	Per Kg	Per Lb.
15	Elliott III	72.6	160	180.3	71	363	143	119	3095	42	19
15	George	63.5	140	181.0	73	134	114	119	3263	51	23
12	Carolyn	56.7	125	172.7	68	258	100	91	2278	40	18
14	Patricia	46.7	103	170.2	67	243	92	73	1997	43	19

on the average 25 5 calories per kilogram body weight per twenty-four hours, and normal women 24 9 calories, an almost negligible difference

Mental activity plays little part in the metabolism of the body, because the total weight of the brain and nerve substance constitutes only about 2 per cent of the body weight Intense mental work, according to experiments by Benedict and Benedict, may raise the basal metabolism some 4 per cent, a trifling factor when compared with the effect of muscular work

Too often in dietetic computations it is assumed that the caloric needs of [illegible]

accentuated. I suspect one will not err greatly if for each mile of walking one allows 1 calorie per 1 kilogram body weight or half a calorie per pound Sewing and knitting require about 9 calories per hour more than that for the same subject sitting quietly in a chair, whereas washing, sweeping and scrubbing floors require 50 calories additional for the actual period of [illegible]

Farmers in various parts of the United States have been shown, before farms were so much mechanized, to consume on an average 3500 calories per day.

One is apt to forget that an individual doing heavy work requires additional calories only for the actual period of that work and not for the entire twenty-four hours With the cessation of work the metabolism falls abruptly. Furthermore, the actual period of heavy work is short and represented by minutes rather than hours If of a pessimistic nature one has only to watch street laborers to be convinced, though a far more enjoyable and as scientific a proof is furnished by the minutes spent in actual play by two football teams In two entire games the minutes in which the ball was in play actually numbered, respectively, eleven minutes and eleven minutes and twenty-three seconds, instead of the supposed four [illegible]

for the last twenty-seven days of his fast of thirty-one days lost an average of 0 7 per cent of his body weight daily, the equivalent of 32.58 calories per kilogram or approximately 1500 calories per pound body weight. For comparison Joslin[16] had an experiment with a healthy nurse who in 1916 volunteered to go through the exact procedure to which diabetics were subjected at that time Her loss of weight in twenty days represented the

[14] Carpenter Jour Biol Chem, 9, 231, 1911

[15] Benedict A Study of Prolonged Fasting Washington, Carnegie Institution of Washington, Pub 203, N 251, 1915

[16] Joslin Diabetic Metabolism with High and Low Diets Washington, Carnegie Institution of Washington, Pub No 323, 1923

equivalent of 3170 calories, 1441 per pound for each kilogram of her body weight lost, and this agrees quite closely with Benedict's fasting subject. Therefore, one must assume that a patient will not lose or, conversely, gain a pound of actual body tissue unless he receives at least 1500 calories less or more food than he requires for his standard met ... computed for rest and ... es of gains ... Dr. Max ... to these estimates and bases his opinion on the work of Strang, McClugage, and Evans[14] who believe the value of a pound of body weight to be nearly twice as much. I cannot reconcile their figures with results obtained by Benedict and myself.

TABLE 51 —THE ENERGY COST OF ACTIVITIES[1]

(Exclusive of Basal Metabolism and Influence of Food)

	Cal per kg per hour		Cal per kg per hour
Bicycling (moderate speed	2 5	Knitting sweater	0 7
Carpentry (heavy)	2 3	Lying still, awake	0 1
Cello playing	1 3	Playing ping pong	4 4
Crocheting	0 4	Piano playing	0 8-2 0
Dancing, foxtrot	3 8	Reading aloud	0 4
Dancing, waltz	3 0	Sawing wood	5 7
Dishwashing	1 0	Sewing	0 4
Dressing and undressing	0 7	Singing	0 8
Driving automobile	0 9	Sitting quietly	0 4
Eating	0 4	Sweeping with broom	1 4
Horseback riding, walk	1 4	Typewriting	1 0
Horseback riding, trot	4 3	Walking rapidly (4 mi per hr)	3 4
Horseback riding, gallop	6 7	Walking (3 mi per hr)	2 0
Ironing (5 lb iron)	1 0	Walking at high speed (5 3 mi per hr)	8 3

... ary staircase with 15 steps, ... staircase of 15 steps, with- ... L P J)

[1] Calculations from Rose Foundations of Nutrition, 3rd ed New York, Macmillan, 1938

The total ... between ... of 132 ... elderly ... , assuming that this is ...

Diabetics require more calories now than formerly Their disease is better controlled and whereas there is less loss of ketone bodies and sugar in the urine, yet they ... greatly impressed wi ... insulin In the forme ...

[14] Strang, McClugage and Evans Am Jour Med Sci, 179, 687, 1930

slowly munching their 5 per cent vegetables, often washed free of carbohydrate, while in the latter period they were sprightly and even boisterous, obviously using more calories

Food Prescribed Versus Food Consumed or Utilized.—The food pre-

patients, his hospital administrator protested) that it led him to isolate his patients for a month at a time, locking the door to guard against caloric indiscretions Thus he was able to prove his point Errors of this nature are far less common now than fifty years ago when self-testing of the urine was far less common, even though Bouchardat in the middle of the last century stressed its importance and even urged patients to analyze the usefulness of a food by testing the urine subsequent to the meal

Food left on the tray, with failure to weigh, record and deduct its value from the diet prescribed, is a very common hospital error which persists Another error, common since the advent of insulin, is to neglect to take

burned by calorimetric determinations This experiment showed that the subject in the
burned carboh
very amounts
In other words
actually eaten
chart In our daily contacts with diabetics less extreme but very great

always be considered in estimating the sensitivity of a patient to insulin

Even though one does not eat food one always consumes body carbohydrate, protein and fat This is illustrated to an extreme degree by F G Benedict s fasting Levanzin who, although he fasted thirty-one days, burned body carbohydrate 69, 42, 39, 4 and 15 grams for the first five successive days of the fast and thereafter almost none Gradually the consumption of body protein fell from 43, 50, 68, 71, 63 grams, to 48, 46, 45 47, 42 grams daily and body fat changed from 135, 142, 130, 136, to 110, 108, 115 grams
my diabeti
that if the
the protein breakdown becomes extreme in the pre-lethal state In my

Richardson Boston Med and Surg Jour, 189, 816, 1923

patient it rose to an excretion of 34.5 grams nitrogen daily, representing a loss of 215 grams protein, or 1075 grams body tissue, each 24 hours in the last six days of life. Fasting in a fat, normal subject is not serious although it can be most harmful in a severe diabetic. On the other hand it is well known that the severe diabetic who ingests no carbohydrate and cannot utilize the 58 per cent carbohydrate moiety in protein may catabolize more fat than he can utilize and the surplus ketone bodies thus released may accumulate and ketosis with diabetic coma result.

Changes in body weight occur even though the caloric value of the diet is constant. Thus if salt is totally omitted the patient will lose a pound or more daily.[17] Similarly striking gains occur with constant calories if the carbohydrate calories are increased and the fat calories lowered, whereas the individual loses weight although calories are still constant but carbohydrate replaced by fat. In the Zuntz experiment[18] on the carbohydrate [illegible] and the average loss per day

[illegible] the commencement of their training is to weigh or measure their food. Today the average level of education in this country has advanced, and we doctors should take cognizance and advantage of it. After a few days of weighing and with the use of measuring cups, patients select utensils which conform to the size of the portions of their own special diets. As a matter of fact, most of our patients use scales at one time or another in the course of treatment. Rolls and the slice of bread vary in weight from year to year.

Carbohydrate.—In teaching diabetic patients their diet, we lay emphasis first on carbohydrate values but also attempt to teach the values for protein and fat. As a rule, we find that patients do not eat too much meat, and as for the fat in the diet, it can be regulated largely by body weight. If a patient will grasp the carbohydrate values of six types of food and use his common sense, he will seldom make egregious errors. See Tables 46 and 47.

Bread.—Bread is the staff of life for everyone and the carbohydrate in it is the chief carbohydrate component of the diabetic diet. It is approximately one-half carbohydrate and the difference in carbohydrate in that made from various flours is not essential save in quantitative studies of the metabolism. Even gluten bread with its lower carbohydrate, +30 per cent, and its increased protein, 25 per cent, makes comparatively little difference. The total quantity rather then percentage of carbohydrate is all important.

[illegible]

codliver oil, 1 tablespoonful daily, or its equivalent or by use of vitamin D milk. It will be seen to be adequate in vitamin A, thiamin, riboflavin, niacin and ascorbic acid. See Table 52.

Cereals.—Oatmeal is the cereal with the lowest carbohydrate content. It is the most voluminous when cooked and therefore the most cherished by

[17] Goodall and Joslin: Arch. Int. Med., *1*, 615, 1908.
[18] Zuntz: Biochem. Ztschr., 44, 290, 1912.

TABLE 52.—COMPOSITION OF FOODS, U S DEPT AGRICULTURE

C—150 P—70 F—75 Calories—1555
Vitamins, Calcium and Iron

Food	Amount Gm	Protein	Calories	Calcium gm	Iron mg	Vit A IU	Thiamine mg	Riboflavin mg	Niacin mg.	Ascorbic Acid mg.
Bread*	90	7.5	218	.08	1.6	—	.22	.14	1.9	—
Orange	150	1.0	49		.4	200	.08	.03	.3	53
Apple	105	0.2	56	.05	.3	80	.03	.03	.2	5
Banana	75	0.6	41		.3	215	.02	.02	.3	5
Oatmeal	30 (dry)	4.2	117	.02	1.4	—	.20	.04	.3	—
Vegetables (4)	150									
Carrots	150	0.9	44	.01	.9	18,000	.07	.07	.7	6
Peas	150	7.5	105	.03	2.8	1,000	.35	.20	3.5	20
Salad Greens	150	2.0	25	.01	1.0	750	.06	.12	.3	15
Tomato	150	1.5	30	—	.9	1,610	.08	.06	.8	35
Milk	300	10.0	196	.35	.2	450	.11	0.50	.30	3
Cream 20%	60	1.6	120	.06	—	480	—	0.08	—	—
Egg	60	6.1	77	.03	1.3	550	.05	0.14	tr	0
(Comb. Beef, Lamb, Poultry)										
Meat†	120	30.0	320	.02	4.9	—	.18	.20	6.8	—
Butter	30	0.1	214	—	—	900	—	—	—	—
Total		73.2 60‡	1,645	.71 1.0‡	16.0 12.0‡	24,355 5,000‡	1.45 1.42‡	1.63 1.5‡	18.1 12‡	142 70‡

*White enriched, 4% non-fat dry milk solids
†Medium fat, medium done
‡N R C recommended allowance moderately active adult in milligrams—thiamin 1.2-1.8, riboflavin 1.8, Niacin 12-18, Ascorbic acid 75
For this Table I am indebted to Mrs Elizabeth K Caso, Nutritionist, Federal Security Agency, Diabetes Section

the diabetic. It is two-thirds carbohydrate. A generous portion would be 1 ounce, 30 grams, dry weight, and thus contains 20 grams carbohydrate. The 1 ounce of dry oatmeal usually amounts to 8 ounces, 240 grams, cooked or in the form of gruel making it about equivalent to the carbohydrate content of milk, namely 5 per cent. Incidentally, it is rich in potassium, as are broths, and this may be one of the reasons our recovering diabetic coma patients by being fed promptly often escape the need of potassium medication. One ounce of dry oatmeal contains protein 5 grams and, unlike other cereals, fat 2 grams. Oatmeal is a standby for a diabetic in health or in illness and, because of its non-irritating qualities, can be taken as strained gruel Portions of other cereals must be substituted in smaller amounts to equalize carbohydrate values, because either inherently richer in carbohydrate or because prepared in a dry state when sold. Roughly most dry cereals are so low in water content that one-sixth less in weight of such, 25 grams, will be equivalent to 30 grams of dry oatmeal

Vegetables.—It would appear perplexing to determine the amount of carbohydrate in each of the various vegetables which the patient eats in twenty-four hours. Diabetic patients have too much to do in their daily work to be encumbered with unnecessary details of arithmetic An attempt to force [illegible]

extent

extent

would seldom eat a sufficient quantity to equal 20 grams carbohydrate in 24 hours.

For convenience we originally classified the vegetables which enter into the diabetic diet under four headings—those containing approximately 5 per cent or less, those containing 10 per cent, 15 per cent and 20 per cent carbohydrate The 15 per cent group of vegetables is small in number, a borderline group, depending to quite an extent upon their age and degree of ripeness Therefore it has been eliminated One could place in this group certain varieties of full-grown green peas, parsnips and young lima beans, but some of the analyses of the latter even exceed it. With such wide variations it seems wiser to class them either with the former 10 per cent, now classed 6 per cent *utilized*, or the present 20 per cent vegetables In the 20 per cent group the following items are included· potatoes, shell beans, baked beans, lima beans, green corn, boiled rice, and boiled macaroni For a discussion of levulose in various foods see page 270 and Table 48, on page 246

Potatoes contain approximately 20 per cent carbohydrate[1] Potatoes baked contain 22 per cent carbohydrate and boiled, if peeled before cooking, 19 per cent French fried potatoes contain 52 and potato chips 49 per cent! Hash browned potatoes contain 32 per cent, but mashed potatoes only 17 per cent even with milk added. A potato the size of an egg contains about 10 or 12 grams of carbohydrate The protein varies from 2 per cent in the boiled to 5.4 per cent in French fried and 6.7 per cent in potato chips Fat is negligible save that in French fried it is 19 per cent, hash browned 12 per cent, but in mashed only 0.7 per cent *In potato chips it reaches* 37 per cent Evidently baked and boiled potatoes are the most desirable if the diet is to be reckoned with accuracy If the potatoes are boiled with

[1] Boulin used potatoes freely because they contain no protein and no fat

the skins on, the loss in protein and mineral matter is slight, but if soaked in cold water before boiling, the loss of protein may reach 25 per cent and mineral matter 38 per cent. Sweet potatoes contain 34 per cent carbohydrate baked and 28 per cent boiled It is not so much the potato alone

relieves the patient

others are eating

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even in fresh fruit vary Fresh grapefruit is rated at 10 per cent although in some varieties more nearly 7 0 per cent Grapefruit juice is 9 per cent and canned, unsweetened 10 per cent but sweetened 14 per cent and grapefruit juice concentrate frozen 38 per cent Strawberries raw contain 6 to 8 per cent, but frozen 27 per cent. Oranges contain 11 per cent carbohydrate and are the most desirable of the fruits, but even in oranges the percentages of carbohydrate are variable.

As for apples, there are few more graphic illustrations of the change in the dietetic treatment of diabetes than my attitude toward them. In the Naunyn and Allen eras, I (E P J) never dared to give them to a child, because they were such a temptation and, unlike oranges, they left no telltale residue The diabetic catechism even included the question "What are you to do with an apple?" and the answer, "Give it away " Today the

not only vary greatly in size, but the range in carbohydrate is from 7 to 16 per cent and it is safer to reckon them as 15 per cent Apples are to be compared to *peeled* oranges and then roughly reduced ⅓ in size because they are 15 per cent and oranges 10 per cent carbohydrate In comparing the size of an orange with that of an apple, a diabetic often forgets he does not eat the thick skin of the orange It is safer to take raw fruits than juices Orange and grapefruit juice contain 10 per cent carbohydrate in contrast to prune and grape juice which contain 20 per cent

Bananas--Bananas are useful for diabetic patients and bananas years ago weighed without the skin about 100 grams Today they are less uniform in size and larger Today the carbohydrate in a slice of bread corresponds more nearly to half a banana Similarly it is safer to prescribe in the early days of treatment bread than potatoes, because one can visualize more readily comparative sizes

Milk--The carbohydrate in milk is in the form of lactose and can be reckoned at 5 per cent, or 1 5 grams per 30 cc , or 1 ounce It is the same in skimm

cent, or 1.

the same

amount o ... are made from whole milk and con-

tain the full amount of fat. Fermented milk may contain 3 per cent sugar. In the last generation the good results of a "skimmed milk cure" in middle-aged diabetics are easily attributed to the undernutrition which it represented. One quart of milk contains between 600 and 700 calories and skimmed milk one-half as much.

Milk contains so many valuable food elements that it is essential to insert some of it as milk, cream, or cheese into the diet. Without milk or milk products it is practically impossible to provide an adequate calcium intake. Four ounces (120 grams) of milk contain carbohydrate 6 grams, and the same quantity of 20 per cent cream carbohydrate 4 grams; thus ½ pint of equal parts milk and cream contain 10 grams of carbohydrate—a useful [illegible] lavin are found to an [illegible] itamin D is availalbe. [illegible] —The metabolism of [illegible] for this account I am indebted to Dr. Albert E. Renold. Also, I would refer to articles by Jorde and Stuhlfauth in "Insulin und Insulintherapie," 1956.[19,19a]

Only those who treated diabetes before the advent of insulin can realize the importance we attached to the utilization of a few grams of carbohydrate Frequently in the Allen Undernutrition Era children lived upon [illegible]

of which about 90 grams is fat, 10 grams is protein, and 14 grams is carbohydrate After the patient has been sugar-free for one or two weeks, his diet is increased to about 1400 calories, of which 140 grams is fat, 28 grams is protein and from 15 to 20 grams is carbohydrate." The possibility *therefore, of the addition of 10, 20 or even 50 grams of carbohydrate to the* total diet of a diabetic, without harm to the patient, knowing it would be metabolized, lead to the formation of glycogen, raise the respiratory quotient and spare protein would have seemed to us a dispensation from Heaven We hoped for this from levulose or its precursor, inulin, in artichokes[20] 30 years ago but never were able to prove to our satisfaction that they were practically *utilizable.*

[illegible] by its optical activity, by being a [illegible] s expense bars it from use in pure [illegible] ol, which is a polyalcohol, resulting from the hydrogenation of glucose or fructose is at present more of a waste product and available for food Sorbitol is absorbed from the intestine even more slowly than fructose *Like fructose, it is metabolized almost* [illegible]

depends somewhat upon the quantity of glycogen already stored in the liver It is greater in the fasting animal There are individual differences.

[19] Jorde Insulin und Insulintherapie, München, Urban u Schwarzenberg, p 136, 1956

[19a] Stuhlfauth Ibid, p 145

[19b] Newburgh and Marsh Arch Int Med, 26, 647, 1920

[20] Carpenter and Root Arch Int Med, 42, 64, 1928.

Sorbitol at present comes as a 70 per cent solution. A teaspoonful [illegible]

3 grams, four times. Sorbitol, like levulose, is so sweet that our diabetics of long duration, who have gone so many years without sweet foods, dislike the sweet taste. These patients add a few drops of lemon juice to each dose. One should not expect a miracle from the use of levulose or sorbitol but if the patients can gain 10, 20 or even 30 grams of carbohydrate independently of the necessity for the use of insulin, that would be of great advantage. Seldom would it be worth while to prescribe sorbitol if the total retained carbohydrate in the diet exceeds 150 to 200 grams.

The objects to be obtained by the use of levulose or sorbitol are to increase the carbohydrate in the diet because that will allow one to reduce the quantity of fat, lower ketogenesis and incidentally perhaps lower the [illegible]

warning of a reaction. Just as glucagon was used in the treatment of reactions with the children at our Camps last summer, so too we have in mind the possibility of using sorbitol this summer. It would be easy to compare the reactions developing if it was employed every other week.

In any use of levulose or sorbitol one must consider that diabetic patients already are receiving considerable amounts of levulose in fruits and vegetables. If they take an orange I would estimate they receive at least 3.8 grams of levulose. In vegetables the per cent consumed is questionable. See Tables 48, 144.

In a basic diet the total amount of levulose may vary from a few grams to as much as 30 or 40 grams, depending upon the amount of honey, cane sugar or fruit ingested. If honey is used the quantity of levulose would be variable. In one kind a tablespoonful weighed 14 grams and contained glucose 4.8 grams and fructose 5.6 grams. Sorbitol is preferable to honey because it contains no glucose with the fructose.

Protein and Fat. – Protein in the diet of a diabetic is practically the same as would be advised for a similar non-diabetic individual. It varies not only according to age with its necessity for growth, but also according to the patient's activity and the condition of the kidneys, an increase of 10 to 20 per cent above standards for the general population is probably desirable. But in all our prescriptions of diets for diabetics, total calories count more than the percentages of carbohydrate, protein and fat, unless these are extreme. There is more justification for this now than before because we recognize more clearly that protein contributes liberally to the intermediaries in the carbohydrate pool which can be built up into glycogen and fat and body tissue or oxidized for heat and energy. It varies from 5 to 2

grams per kilogram body weight for the infant and child, and 1.75 to 1

ld fall below 0.66 grams per

extra protein allows a little

d beds in hospitals respond

quickly to liberal protein diets. They need the same for wound healing

Advances in the knowledge of proteins in the last fifty years, and partic-

discussed in the Chapter on Physiology page 107 and their special application to diseases of the liver on page 469, of the kidneys on page 429, and to burns, trauma and surgical problems on page 589. Suffice it to say here that the emphasis of modern thought is to give more rather than less protein

are tryptophane, phenylalanine, lysine, threonine, valine, methionine, leucine and isoleucine The minimum requirements of each have been determined and vary from 0 25 grams daily for tryptophane to 1.1 grams for phenylalanine The level of amino acids in the plasma is fairly constant although ingesta and excreta do not balance Yet, for protein synthesis all these essential amino acids must be present at one time in the body and for optimum utilization by the tissues at least 20 per cent of the nonessential amino acid nitrogen also should be present in the diet. All of these factors are especially important in intravenous protein therapy which is by no means superior to oral therapy, and in fact, utilization is less efficient. Recently the part played by amino acids has again come under discussion, see page 274

Recent work points to the advantage of a liberal protein diet in hepatic disease. And we all recognize the spectacular effect of the giving of liver

creases to 1 gram or even 0.66 for the aged

I noticed that my uncle at ninety-four was more than satisfied with that

by furnishing an abundance of calories as carbohydrate and fat, and Karl Thomas by frequent feeding lowered the same to that represented by an *excretion of 2 and 3 grams of nitrogen, but this is no proof that it is desirable* to do so When Professor Russell H Chittenden was experimenting with a low protein diet on his own person, my father noticed he took at least 3 lumps of sugar to a *demi tasse* of coffee

Vegetable proteins are said to give rise to less carbohydrate in the diabetic organism than do animal proteins As a matter of fact, carbohydrate

may be formed out of any protein On the other hand, animal protein has a higher biologic value than vegetable protein. Gelatin is lacking in the amino acids, tryptophane, tyrosine and cystine, and thus is not as adequate a protein as is found in meat, milk and fish although this does not appear to prevent its curative action in the treatment of cracked finger nails

according to whether it is cooked or uncooked, and also as to the amount of fat. Normally, the protein can be reckoned as 7 to 8 grams per ounce cooked meat. See Table 48. Cheese and nuts vary greatly in protein depending also on the presence of fat In exact studies each variety must be estimated by analysis or by consulting the published tables See page

Gluten breads vary in composition, carbohydrate 33 to 53 per cent, protein 8 2 to 11 1 per cent. Nuts like many kinds of cheese are highly concen-

fat than most other fish, showed in its analysis only 16.5 per cent fat, cooked 5 2 per cent, canned on the average 8 5 per cent; shad 9 8 per cent; and herring raw 2 6 per cent, but smoked or kippered 12 9 per cent; and mackerel 12 per cent. In general, other kinds of fish show 6 per cent or less of fat Halibut steak, for example, contains 7 8 per cent, and cod raw 0 4, dried 2 8 per cent. Preserved fish, however, is quite rich in fat; thus sardines contain 11 to 27 per cent and fortunately the content of unsaturated fats is high

Shell-fish make agreeable additions to the diet (1) They are desirable because they are palatable; (2) they are usually bulky foods and so are

contain about 9 grams protein, 2 grams fat and 5 grams carbohydrate—the equivalent of 74 calories Clams on the shell contain a trifle more protein, but about half as much carbohydrate and fat Lobsters are ideal for a diabetic because of their low protein and negligible fat

Broths in the days of undernutrition were a real factor in the diet As

before serving, and may be as low as 0 1 per cent The amount of carbohydrate is negligible, 0 2 per cent or less. For practical purposes calorically, therefore, broths are allowable, but in metabolism experiments and in the presence of edema, because of their high content of salt, they must be ex-

cluded. In coma, they are almost life-saving because of their content in sodium and potassium, their tolerance by the stomach, and the desirability of giving hot liquids The salt varies greatly, from 2 per cent to 0.1 per cent. The potassium in a cup of broth is equivalent to about 250 mgs. of potassium chloride. It is a good deal cheaper to use broths in diabetic coma than to give liquids intravenously, and quite possible to do so with good nursing and limitation of liquids at first, soon after lavage of the stomach, to 50–100 cc. an hour.

[illegible]

serine.

The fate of lysine, valine, histadine and tryptophane is obscure. *Tryptophane is the one amino acid we must all have to maintain nitrogen equilibrium.*

Fats.—The changes in the conception with which the metabolism of fat is now regarded compared to the early days of this century are very great. At present we know that ketone bodies derived from fat normally enter into the metabolism and are of the greatest importance unless their production is extreme. Fat contributes to the metabolic pool and it is not hard to visualize this, because of the similarity of the formulae of diacetic acid (CH_3 CO CH_2 COOH), lactic acid (CH_3 CH OH COOH), and pyruvic acid (CH_3 CO COOH).

The quantity of fat in the normal diet varies, partly from choice and partly from economic reasons. In general, in those cases where the carbohydrate in the diet is high, the fat is low, and *vice versa*. The average in a series of 1300 dietary studies among different races and in different climates was about 135 grams fat per person per day, the variation being from 45 to

[illegible]

margarine is fortified for the lack of vitamins by law. The oils commonly used are very poor in vitamins, except such medicinal oils as from the livers of cod and halibut. Fat is also a concentrated food, not only because it has twice the caloric value of either carbohydrate or protein, but because it occurs more frequently in pure form. Oil, butter and lard contain little water, whereas, except for pure sugar and starch, most carbohydrates and *proteins are diluted five to ten times with water.*

The chief source of error in calculating the total caloric value of the diet, and especially of the diabetic diet, is in the estimation of fat. It is difficult [illegible] On the average, [illegible] ent or about [illegible] correct for [illegible] of fish, such [illegible] one had best [illegible] e patient is [illegible] 37 to 79 per cent in specimens we have examined and we have adopted 50 per cent as an average value.

Eggs in some cities by law must weigh 1½ pounds a dozen, and average 60 grams (2 ounces) apiece. Such eggs contain approximately 6 grams of protein and 6 grams of fat. How gross our caloric reckonings are is obvious if a collection of eggs is weighed and the minimum and maximum weights noted. The weight of the heaviest egg in a collection of 50 was 72 per cent more than that of the lightest. The weight of egg-shells is usually about 7 grams.

The quantities of fat in milk and cream, milk products, the various cheeses and nuts are so considerable that even for clinical accuracy the amounts allowed must be verified.

[illegible]

diabetic food because they constitute pure fat, have a tendency to lower the cholesterol, are agreeable, and have maximum caloric value for their bulk. Italian patients naturally bear olive oil unusually well.

Our American non-diabetic diet contains about 25 to 35 per cent of the calories as fat in contrast to our suggested preliminary, simple diet, Table 46, which contains about 40 per cent fat calories. Therefore, it is desirable when possible to lower the fat. This can be done and yet maintain sufficient calories if the carbohydrate and protein can be raised. Any possible harm from the 40 per cent fat in the diet also can be counteracted to some extent, as will later be mentioned, by the substitution of fats containing unsaturated instead of saturated fatty acids. See page 281. If we only raise [illegible]

oil a distinct impression is made on the fat ration.

The Value of Fat to the Diabetic.—In the first twenty years of the century fat provided the bulk of the diabetic patient's calories, far more than the 40 per cent in the proposed simple preliminary diet. It is surprising how readily double and even treble the quantity of fat ingested by normal individuals was borne by the stomach of the diabetic patient and what is of far more significance is the fact that our 82 Quarter Century Victory Medal Diabetics, with their sound bodies, perfect eyes and arteries, were exposed in the first few years after onset of their diabetes to diets proportionately much higher in fat than those of today. Perhaps this was counterbalanced by the low total intake of calories. Time will tell whether the superior condition of these patients after twenty-five years was due to the low-carbohydrate high-fat diet, the rigid control of the diabetes, or was associated with the low total metabolism, all measures tending to rest the pancreas. Certainly those Victory Medal Cases stand as a challenge to any patients or doctors who advocate other types of treatment. We do know that tolerance for carbohydrate is less when the patient is on a low-

carbohydrate high-fat diet, and yet how important this may be in the ultimate course of the disease is still a subject of discussion.

Only under extraordinary circumstances even in the treatment of a fat *diabetic should the prescribed fat be kept under 50 grams.* Even if the patient does hold down his fat ration to 50 grams, the chances are he will

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a minimum of fat, but it is seldom caloric needs require it to reach or much less exceed 125 grams

Next to the role played by

many mysteries connected wit

tionized our thoughts Toda

derived from fat have a place in normal metabolism, but that the intermediary products of fat and carbohydrate metabolism are not only interchangeable but that fat, far from being a stable and static tissue, wanders rapidly about the body and can rise and fall in the liver two- and three-fold in twenty-four hours

By administration of insulin, hyperlipemia can be reduced with great rapidity. In the case reported by Rabinowitch[n] extreme lipemia was eliminated in the course of a few hours by intensive insulin therapy. It was estimated that this patient lost from the blood one pound of fat over night following institution of treatment and another pound the next day.

It is unreasonable to give less fat to a diabetic than to a non-diabetic or *more than the patient can take without developing acidosis or an elevated* cholesterol Probably an amount sufficient to bring the weight up to 10 per cent below normal is adequate, except in younger individuals who should be of normal weight.

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Newburgh and Marsh and Petrén courageously demonstrated that patients did not die in the hospital while living upon a high-fat, but low-carbohydrate and very low-protein diet, even before the explanation therefore was perfectly plain, namely, undernutrition and a low metabolism.

Fat in any form is absorbed by the diabetic patient very well, but probably in more cases than supposed it has escaped absorption due to a deficiency in the external secretion of the pancreas as Chester Jones[114] has demonstrated It also escapes absorption in those rare cases of diabetes with general pancreatic involvement One such case (Case 670) was seen by me a few days before coma In this instance diabetes occurred after partial loss of the gland from acute pancreatitis The case was reported *in detail by Jurist* [115]

[n] Rabinowitch and Peters Am Jour Med Sci, *178*, 29, 1929
[114] Jones, Castle, Mulholland and Bailey Arch Int Med, *35*, 315, 1925
[115] Jurist Am Jour Med Sci, *133*, 180, 1900

Fat, however, is not well absorbed by the dog made diabetic by the removal of the pancreas. This fact explains one of the difficulties experienced in producing acidosis in dogs. If trypsin is given and protein utilized, the percentage of glycosuria rises, thus opposing the idea that the loss of the alpha cells lessened the severity of the diabetes after complete pancreatec-

tion of the pancreatic gland in some form in order to prolong life beyond eight months. Apparently this is not due merely to defective fat absorption, but to defective fat metabolism in the liver, and this is caused not by lack of feeding pancreas or even its component lecithin, but by absence of the choline portion of the lecithin molecule.

Cholesterol.—Cholesterol may be increased in uncontrolled diabetes,

that ninety per cent of the cholesterol metabolized daily in the body is synthesized by the body itself. This is good proof to me that cholesterol is a necessity. Furthermore, a low cholesterol, 100 mg. or less in the blood plasma, is a precursor of death in a few weeks. Cholesterol values for normal human subjects are shown in Table 53.

TABLE 53.—BLOOD LIPIDS IN NORMAL HUMAN SUBJECTS

(Values are expressed as mg. per 100 cc. plasma)

Authors	*Year*	*Total Lipid*	*Neutral Fat*	*Phospholipid*	*Cholesterol*	
					Total	*Free*
Man and Peters[1]	1933	659		222	207	
Boyd[2]	1935	582	131	185	177	52
Page *et al.*[3]	1935	735	225	181	232	82

[1] Man and Peters: Jour. Biol. Chem., *101*, 685, 1933.
[2] Boyd: Ibid., 323, 1933; Ibid., *110*, 61, 1935.
[3] Page, Kirk, Lewis, Thompson and Van Slyke: Ibid., *111*, 613, 1935.

Insulin has made the diabetic so nearly a normal individual from a metabolic point of view that today we do not see many patients who show gross abnormalities of fat metabolism. In Table 54 are recorded values for cholesterol in the blood of our diabetics as given for the years 1916 and 1917, when Professor Bloor assisted us so much and subsequently when Dr. Horace Gray and Miss Hazel Hunt were associated with us.

The values shown in Table 54 are undoubtedly somewhat higher than for the average of all our diabetics treated in each of the various periods

[a] Allen: Ibid., *154*, 313, 1917.

carbohydrate high-fat diet, and yet how important this may be in the ultimate course of the disease is still a subject of discussion.

Only under extraordinary circumstances even in the treatment of a fat diabetic should the prescribed fat be kept under 50 grams. Even if the patient does hold down his fat ration to 50 grams, the chances are he will consume enough fat of his own body to increase the fat metabolized. A diabetic always eats (!) even if compelled to eat his own body fat A diabetic likes fat almost more than carbohydrate, or at least craves more than a minimum of fat, but it is seldom caloric needs require it to reach or much less exceed 125 grams.

Next to the role played by glycogen is that played by fat, and there are many mysteries connected with it. Stadie's and Stetten's work has revolutionized our thoughts. Today, we realize not only that the ketone bodies derived from fat have a place in normal metabolism, but that the intermediary products of fat and carbohydrate metabolism are not only interchangeable but that fat, far from being a stable and static tissue, wanders rapidly about the body and can rise and fall in the liver two- and three-fold in twenty-four hours

By administration of insulin, hyperlipemia can be reduced with great rapidity. In the case reported by Rabinowitch[21] extreme lipemia was eliminated in the course of a few hours by intensive insulin therapy. It was estimated that this patient lost from the blood one pound of fat over night following institution of treatment and another pound the next day.

It is unreasonable to give less fat to a diabetic than to a non-diabetic or more than the patient can take without developing acidosis or an elevated cholesterol. Probably an amount sufficient to bring the weight up to 10 per cent below normal is adequate, except in younger individuals who should be of normal weight.

Enormous quantities of fat were given formerly: thus, Case 314, age at onset 40 years, took 372 grams of fat on an oatmeal day, September 15–16, 1910, and lived 8 years The acidosis on this day was extreme, as shown by the excretion of 27 6 grams beta-oxybutyric acid. Many diabetic pa-
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tients did not die in the hospital while living upon a high fat, but a carbohydrate and very low-protein diet, even before the explanation therefore was perfectly plain, namely, undernutrition and a low metabolism.

Fat in any form is absorbed by the diabetic patient very well, but probably in more cases than supposed it has escaped absorption due to a deficiency in the external secretion of the pancreas as Chester Jones[21a] has demonstrated It also escapes absorption in those rare cases of diabetes with general pancreatic involvement One such case (Case 670) was seen by me a few days before coma In this instance diabetes occurred after partial loss of the gland from acute pancreatitis The case was reported in detail by Jurist[21b]

[21] Rabinowitch and Peters Am Jour Med Sci, *178*, 29, 1929
[21a] Jones, Castle, Mulholland and Bailey Arch Int Med, *35*, 315, 1925
[21b] Jurist Am Jour Med Sci, *139*, 180, 1900

12 others were included 2 with tuberculosis, 1 with pernicious anemia, 3 with other endocrine disorders, and 3 cases of severe juvenile diabetes. Even without the existence of diabetes a low cholesterol content of the blood could occur with most of these conditions, particularly tuberculosis or sepsis. Although it is likely that the low cholesterol in diabetic patients with such diseases is associated with the response of the body to the complications rather than to diabetes itself, the rôle of the latter may be im-

of our patients formerly died. Of 137 coma cases whose blood lipids were studied at the New England Deaconess Hospital from 1926 to December, 1939, only 24 showed a marked increase of blood cholesterol. The highest blood lipid value we have ever found in coma was in Case 9629, whose lipid was 19.9 per cent and whose cholesterol was 1.42 per cent. This patient did not recover. Acidosis and coma are not always associated with high blood lipid values. In our series 50 per cent of the coma cases had cholesterol values which were normal or only slightly above normal at the height of the acidosis. Only 5 per cent of the cases had markedly elevated cholesterol values which did not return promptly to normal with therapy. The height of the cholesterol does not seem to be dependent upon the severity of the acidosis.

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1580 mg. per cent, respectively, had cholesterol values of 370 and 348 mg. per cent. Both of these patients recovered. Case 4099, lived six years and Case 6884, nine years after this attack of coma. In a group of 43 cases with abnormally high blood cholesterol, the average value for the cholesterol was 557 mg. per cent but the average blood sugar was only 0.24 per cent.

The blood cholesterol, whose response to insulin is not as prompt or as spectacular as the blood sugar, is in some respects, a more reliable index of the fundamental clinical condition than is the blood sugar, which reflects a temporary state. Particularly is this true if one is dealing with a single isolated value.

Although the cholesterol in the blood is by no means wholly dependent on the cholesterol in the diet, it is of interest to know its percentage in various foods and this is shown in Table 55.

Fat and Its Relation to the Prevention of Atherosclerosis in Diabetes.—Diabetics are known to be more prone to atherosclerosis than non-diabetics

a diabetic heredity. In the average American diet fat constitutes not far from 35 to 40 per cent of the total calories but in the usual diabetic diet,

because, in general, tests were performed when we expected them to be abnormal. In those years, 1915, 1916, and 1917, Dr. Francis G. Benedict and I were studying the metabolism of diabetics treated with extreme undernutrition. The cholesterol values fell in successive years and coincidentally the duration of the diabetic life of our patients rose. In 1914–1922, the average duration of diabetes in our fatal cases was 6.1 years, in 1922–1929, it was 8 years and 1930–1936, it was 10.3 as compared with 18 years in 1957.

TABLE 51.—TRENDS IN CHOLESTEROL VALUES IN AUTHOR'S DIABETIC PATIENTS

Year	Investigator	Analyses	Cases	Cholesterol mg per cent (avg values)
1916	Bloor	36	Adults	360
1917	Bloor and Gray	131	Adults	385
1921	Gray	1062	Adults and Children	290
1927	Hunt	335	Adults and Children	257
1930	Hunt and White	110	Children	211
1932–1939	Hunt	5196	Children and Adults	214

Of 2200 selected diabetics whose blood was studied for cholesterol content during 1935–1939, there were only 93 whose values exceeded 400 mg. per cent, and of these, in 68 cases the cholesterol was high, quite apart from coma or acidosis. Among these 68 cases there were 22 instances with diabetes beginning in childhood, and only 1 of these 13 cases studied carefully failed to exhibit a serious complication of diabetes, such as cataracts, arteriosclerosis, abscesses, retinitis, lipemia retinalis. The diabetes in these children was uncontrolled and these complications demonstrate what is likely to happen to the carelessly treated diabetic. Seventeen of the 22 patients were girls. There were 3 adolescents with high cholesterol values above 400 mg. per cent. One of these died of lipoid nephrosis and another had xanthoma. The third, Case 6593, appeared in good condition but his cholesterol was 325 mg. per cent in November, 1934; he was reported alive in July, 1951, although he had developed tuberculosis in 1942, but is living in 1958.

Forty-three adults had cholesterol values apart from coma which were above 400 mg. per 100 cc. of blood. Among these the complications were arteriosclerosis, retinitis or cataracts, xanthoma, and a variety of other conditions such as gangrene, carbuncles, jaundice and gall-stones. In other words, for practical purposes a cholesterol consistently above 400 mg. per cent in a diabetic implies that serious complications exist or are imminent.

A low cholesterol, apart from those in patients under one year of age, is a serious cholesterol. Patients with values of 90 mg. per 100 cc. of blood or under have shown the shortest duration of life after the test and the

3 pernicious anemia, 2 endocrine disturbances of pituitary origin, 1 hemochromatosis, 1 a calcified pancreas, and 1 cirrhosis of the liver. Among the

12 others were included 2 with tuberculosis, 1 with pernicious anemia, 3 with other endocrine disorders, and 3 cases of severe juvenile diabetes Even without the existence of diabetes a low cholesterol content of the blood could occur with most of these conditions, particularly tuberculosis or sepsis. Although it is likely that the low cholesterol in diabetic patients with such diseases is associated with the response of the body to the complications rather than to diabetes itself, the rôle of the latter may be important and deserves further investigation.

The influence of acidosis upon blood lipids is evident because it was due to abnormalities in fat metabolism that so great a percentage—64 per cent—of our patients formerly died Of 137 coma cases whose blood lipids were [illegible] December, [illegible] The highest [illegible] 629, whose lipid was 19 9 per cent and whose cholesterol was 1.42 per cent. This patient did not recover Acidosis and coma are not always associated with high blood lipid values. In our series 50 per cent of the coma cases had cholesterol values which were normal or only slightly above normal at the height of the acidosis Only 5 per cent of the cases had markedly elevated cholesterol values which did not return promptly to normal with therapy The height of the cholesterol does not seem to be dependent upon the severity of the acidosis

There is no close parallelism between blood sugar and blood cholesterol values Especially is this true in extreme cases Case 12383, with a blood cholesterol of 1600 mg per cent and lipemia retinalis had a blood sugar of 0 21 per cent, whereas the 2 patients who have had the highest blood sugar of our group, Case 4009 and Case 6884, with blood sugar values of 1600 and 1580 mg per cent, respectively, had cholesterol values of 370 and 348 mg per cent Both of these patients recovered. Case 4009, lived six years and Case 6884, nine years after this attack of coma In a group of 43 cases [illegible]

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Fat and Its Relation to the Prevention of Atherosclerosis in Diabetes—Diabetics are known to be more prone to atherosclerosis than non-diabetics and atherosclerosis is acknowledged to be closely related to fat. One is on safe ground therefore, in making every effort possible to prevent obesity and to treat it aggressively in its [illegible] even for the prevention of big ba[illegible] a diabetic heredity. In the avera[illegible] from 35 to 40 per cent of the total calories but in the usual diabetic diet,

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The quality of fat in the diet counts. This was pointed out and emphasized by Kinsell[23] who showed that a diet with unsaturated fatty acids, chiefly of a vegetable nature, would lower the cholesterol as compared with a diet of the saturated fatty acids, chiefly in meat and milk products. Furthermore, vegetable sitosterols will lower the absorption of cholesterol and such are on the market. The literature upon the subject is voluminous and bewildering. One of the simplest demonstrations is by Malmros[24] who showed in animals and humans that the cholesterol was lowered with a diet utilizing corn oil instead of coconut oil. Fortunately, excellent summaries by Stare[25] and by Keyes[26] upon the effect of saturated and unsaturated fatty acids in various nations, races and under various circumstances have appeared for the guidance of doctors generally. Through the courtesy of Professor Stare I am able to print the following table in which unsaturated fatty acids, fats in borderline stages and saturated fatty acids are shown. Table 56.

Despite data which suggest that diets containing relatively large amounts of saturated fatty acids may favor hypercholesterolemia and atherosclerosis, it is probably premature to advise a radical revision of the American dietary. This was the conclusion of a special committee of the American Heart Association.[26a] However, the following suggestions seem both reasonable and practical, at least in the planning of diets for diabetic patients and their relatives. (1) Total fat and total calories in the diet should be low enough to prevent overweight. (2) The amount of total calories furnished by fat should, if feasible, be kept at 40 per cent or less, utilizing insulin, exercise and perhaps sorbitol (levulose) to increase the proportion of carbohydrate in the total diet. (3) Whenever possible unsaturated fats (usually liquid fats of vegetable origin) should be used, both in cooking and at the table in place of saturated fats (usually solid fats of animal origin).

Finally, let us not forget as already stated, that our patients are living 18 years with diabetes instead of 5 years and therefore, we are encouraged to continue present methods with slight modifications which promise even better results.

Other means may be used for the reduction of the blood cholesterol, namely, extracts of certain endocrine glands. Medication with thyroid

[23] Kinsell. Am. Jour. Clin. Nutrition, 3, 247, 1955.
[24] Malmros. Lancet, 2, 1, 1957.
[25] Stare, Van Itallie, McCann and Portman. Jour. Am. Med. Assn., 163, 1920, 1957.
[26] Keyes. Mod. Med., 25, 78, 1957.
[26a] Page, Stare, Corcoran, Pollack and Wilkinson. Circulation, 16, 163, 1957.
[26b] Parsons et al. Proc. Staff Meet. Mayo Clin., 31, 377, 1956.
[26c] Goldner and Vallan. Am. Jour. Med. Sci., 236, 341, 1958.

somewhat more. Thus, the aim is to lower the calories dependent on the metabolism of fat.

Since the introduction of insulin, as shown in Table 54, the average cholesterol in the blood serum of diabetics has dropped materially. Exercise, by promoting the oxidation of carbohydrate, also helps in this reduction. If with the use of levulose, which is known to be tolerated by diabetics without increasing the blood sugar or appearing in the urine, the carbohydrate could be raised 10, 20, or 30 grams, the fat could be correspondingly decreased It is hoped this can be done by the use of sorbitol.

TABLE 55.—CHOLESTEROL CONTENT OF FOODS*

Food	*Cholesterol Mg per 100 gm*	*Food*	*Cholesterol Mg per 100 gm*
Beef brain	2360	Eggs, dried whole	2140
Heart	150	Dried yolk	3900
Kidney	400	Fresh whole	468
Liver	260	Fresh yolk	2000
Lung	300	Frog	40
Muscle	60	Hen	70
Round, medium fat	1250	Lamb	70
Round, lean	950	Oysters, eastern	230
Thymus (sweetbreads)	250	Pigeon	110
Brewers' yeast, dry	680	Pork	60
Butter	280	Pork, spareribs	105
Casein, raw	65	Primex	150
Cheese, cheddar (American)	160	Rabbit, wild	80
Cheddar (American) processed	155	Salmon	60
Limburger, processed	135	Shrimp	150
Monterey, Jack	190	Turtle	60
Pimento, cream	140	Veal, breast	100
Swiss, processed	145	Muscle	65
Velveeta	160	Shank	140
Duck	70		

*From Okey Jour Am Dietet Assn, *21*, 341, 1945

All food from animal sources is assumed to contain some cholesterol Those listed here are the only common foods for which reliable figures are given to date

For an index of the metabolism of fat in the body the most practical component is the blood cholesterol, particularly because of the different lipids this analysis is the simplest Investigators, who have been especially interested in the lipoproteins, value its use as an index Other possibilities *are the determinations of linoleic acid and recently the possibility arises that* the non-esterified fatty acids might serve in this capacity However, today for practical purposes the cholesterol is our best guide

Determinations of blood cholesterol vary greatly according to the time they are taken, the duplications of results in the same laboratory several hours after the first determination, and above all, in different laboratories This has been strikingly proved recently [22] One should know the errors in one's own laboratory and compare results not only in this laboratory from time to time but with those in other laboratories It certainly is to be hoped

[22] Rivin, Yoshino and Shickman Jour Am

may go awry and too much insulin be produced and, in fact, so much that at times death may result from hypoglycemia. Probably at one time or another all of us experience symptoms from an increased production of pancreatic activity which we recognize in ourselves by hunger and fatigue and our friends suspect by our altered disposition.

variety and quantity according to the need as shown by the results of tests of urine and blood before each of the meals and at bedtime.

If the patient is seen in the morning, the dosage can be increased in frequency and quantity before each meal or every few hours as is done in the treatment of diabetic coma. Less haste would be employed in the elderly diabetic. In all cases the patient should be forewarned about temporary changes in vision as the glycosuria falls. Insulin can be increased slowly or rapidly depending upon how close will be the observation of the patient and the opportunity for the prevention of his undergoing a severe reaction. A mild reaction is often advantageous. So admirable a clinician as the late Bertnard Smith of Los Angeles always planned for his patients to experience it.

A single injection of a long-acting insulin is desirable and will suffice for

before the evening meal, or less conveniently before the noon meal.

Diet, exercise and insulin are all variables and in general the rule is to change only one of the three at a time.

There are three types of insulin, those with "quick," "slow" and "intermediate"

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diabetes in the adult seldom made this necessary.

Since the rise in per cent of sugar in the blood after a meal reaches its peak in about half to one hour and the action of the "quick" insulin is at a maximum in 60 minutes after injection, regular insulin is usually administered half an hour before a meal. If the intake of food is delayed, a low

of Vitamin C, Rauwolfia, metrazole and pyridoxine reduced the severity of the side effects of niacin. However, longer experience with this substance will be necessary before definite therapeutic evaluation is possible.

TABLE 56.—APPROXIMATE FATTY ACID COMPOSITION OF A FEW SELECTED FOODS*† 100-gram portions

	Saturated	Monounsaturated (mostly oleic acid)	Polyunsaturated (mostly linoleic)
Oils			
coconut	91.5	6.0	2.5
corn	11.7	46.0	42.3
cottonseed	25.1	21.7	49.7
olive	10.0	82.8	7.2
peanut	19.0	60.0	21.0
safflower	6.1	26.4	67.5
soybean	11.4	28.0	60.6
Fats			
butter	47.0	25.8	3.9
lard	35.0	47.1	12.9
margerine	11.6	57.3	5.1
Meat, poultry, fish			
bacon, cooked	19.2	27.5	5.5
beef (sirloin raw)	8.4	10.1	.5
beef (round raw)	4.6	5.5	.3
ham, boiled	9.9	16.5	2.9
lamb, cooked	8.8	7.3	.5
turkey, raw	6.0	8.8	5.2
salmon	4.9	5.1	5.4
sardines, drained	3.5	3.0	3.9
Dairy Products			
milk	2.1	1.3	.2
egg	3.4	4.7	2.7
cheese (cheddar)	13.7	8.6	.6
ice cream	6.9	4.2	.8
Others			
Almonds	4.53	39.35	10.27
Avocado	5.05	16.63	3.54
Peanuts (whole)	8.40	22.68	11.81
Walnuts (English)	5.18	10.21	48.64

*Sources mainly from
Hayes, O. B. and Rose, G. Supplementary food composition table. Jour. Am. Diet. Assn., 33, 26, 1957.
Oils and Fats Composition and Physical Properties Chart. New York, Technical Products Division, L. F. Drew and Co., W. d.
†Data supplied through the courtesy of Dr. Frederick J. Stare, Dept. Nutrition, Harvard University, School of Public Health.

The Insulins and Their Administration.—All of us require insulin, and if we cannot manufacture what we need, we are fortunate if we can secure it by purchase or gift. None of us, the normal or the diabetic, knows the quantity required to maintain health and strength. Fortunate it is that Nature regulates the supply with surprising accuracy, balancing its production with the carbohydrate consumed, whether this be for prompt utilization or for storage as glycogen or fat, and adjusting its output to the momentary demands of exercise or rest. This normal regulatory mechanism rarely

blood sugar with an insulin reaction may result. Consequently, patients must always be taught to be prepared for a meal being delayed by having

of infections and after surgical operations If very large doses of regular insulin are used as in the treatment of diabetic coma the duration of its action is prolonged even for 12, 25, or 36 hours

Protamine zinc insulin is the "slow" and longest acting insulin. Its peak action is in 8 to 12 hours and its duration is 24 to 36 hours and to some extent for almost 48 hours Acting so slowly it would not control the effect of the food taken at breakfast unless the residual effect of the insulin taken a day earlier might suffice This could be adequate, especially if the breakfast contained little carbohydrate Consequently, to make a single dose sufficient for the 24 hours might necessitate radical lowering of glucose-

heaviest in the day Quite apart from insulin, it was learned in pre-insulin days that the diabetic's tolerance for food was always least for breakfast, greater for lunch, and most of all before the evening meal Indeed, a few grams, even 5 grams of carbohydrate taken before breakfast makes more utilizable a breakfast eaten one hour later, just as does a little moderate exercise as Case 6669 demonstrated by light work in his garden

Theoretically and practically a great effort should be made to spread the intake of food over as many hours in the day as possible Ordinary hospital meal hours with breakfast at 8:00 A M and supper at 5:00 P M or more commonly 4 30 P M are most detrimental to a diabetic's tolerance Breakfast should be nearer 7:00 A M and the evening meal at 7 00 P M with a noonday lunch, and usually a minimum lunch, to prevent reactions in mid-forenoon,

From the above it is easily understood why a diabetic taking an intermediate insulin should protect himself in the late afternoon from a low blood sugar by eating a little carbohydrate at 4 or 5 o clock when he leaves his work to avoid a reaction before arriving home at 6:00 or 6:30 for his evening meal A prophylactic lunch between meals might be one or two lumps of sugar (5 or 10 grams), or one- or two-thirds of a one-ounce chocolate

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TABLE 57.—INSULINS

Type	*Appearance*	*Action*	*Duration hours*	*mg Zinc 100 units*	*Buffer added*	*Protein*
Regular	Clear	Rapid	5–7	0–04	None	None
Crystalline	Clear	Rapid	5–7	016–04	None	None
Protamine zinc	Cloudy	Very slow	36	.20–25	Phosphate	Protamine
Globin	Clear	Slow	18–20	0–.30	None	Globin
NPH	Cloudy	Slow	26–30	016–04	Phosphate	Protamine
Lente	Cloudy	Slow	26–30	20–25	Acetate	None
Semilente	Cloudy	Rapid	12–18	.20–25	Acetate	None
Ultralente	Cloudy	Very slow	36+	.23–25	Acetate	None

blood sugar with an insulin reaction may result Consequently, patients must always be taught to be prepared for a meal being delayed by having 5 or 10 grams of carbohydrate—one or two lumps of sugar—available as a substitute. If the patient will only learn this fundamental point, together with another that exercise lowers the need for insulin, most of the reactions due to the fall of the blood sugar from insulin can be avoided Regular

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quick action is required, as in the treatment of diabetic coma, in the presence of infections and after surgical operations. If very large doses of regular insulin are used as in the treatment of diabetic coma the duration of its

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The intermediate insulins in order of discovery are NPH insulin, Globin

From the above it is easily understood why a diabetic taking an intermediate insulin should protect himself in the late afternoon from a low blood sugar by eating a little carbohydrate at 4 or 5 o'clock when he leaves his work to avoid a reaction before arriving home at 6.00 or 6·30 for his evening meal A prophylactic lunch between meals might be one or two lumps of sugar (5 or 10 grams), or one- or two-thirds of a one-ounce chocolate bar, the wh

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peanuts 15 (more or less), two in a shell, weighing about one ounce (30 grams), with carbohydrate 6, protein 8, fat 10 grams. These would be about the equivalent of a graham cracker with an ounce of cheese. One man with persistent reactions overcame the same by taking on the hour, when the clock struck, a small 5-gram cracker and when doing heavy work, doubling the same. For a discussion of hypoglycemia see page 314.

Protamine zinc insulin, NPH insulin, Lente insulin, and Globin insulin to a slightly less extent, act during every hour of the day, "act while you

of the 24 hours when the body is without food, the quick-acting insulins supplement control during the eating part of the 24 hours. When the patients take RI or CI they should eat within 30 minutes.

The NPH insulin at the moment appears to be the insulin most universally used in this country. Very similar to it is the modification of Lente insulin known as semi-Lente and Globin insulin. Whereas these intermediate insulins have their peak action in 8 to 10 hours and last for 18 to 2

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insulin, because approximately one-half of the regular insulin changes to protamine insulin as a result of the excess protamine in PZI uniting with the regular insulin. Consequently, allowance must be made for this should such mixtures be adopted. Furthermore, they are less apt to be uniform than would the mixture of regular insulin with one of the intermediate acting insulins.

After operations and during the course of infections a prescription for insulin may be written for its use every 4 hours according to the color of the Benedict's solution test.

Every 4 hours Regular Insulin $\frac{16}{\text{Red}} - \frac{12}{\text{Or}} - \frac{8}{\text{Yel}} - \frac{4}{\text{Green}} - \frac{0}{\text{Blue}}$ units according to test

With many patients the action of NPH insulin during the forenoon is not rapid and strong enough to prevent blood sugar values at two hours after breakfast from rising to quite high levels. Consequently, with most patients a *forenoon lunch* is unnecessary. Contrariwise since the peak of NPH action begins in the afternoon, a *mid-afternoon lunch* should be *given uniformly* and, as with all insulins, *a bedtime* lunch to prevent reactions during the night.

Best[264] states the "action of insulin is to remove all the signs and symptoms of diabetes." To be more specific, insulin takes the carbohydrate as modified by the enzymes adenosine and hexokinase in the carbohydrate

[264] Personal Communication

pool, whether derived from carbohydrate, protein or fat, and regulates its deposition as glycogen in the liver and muscles and its release by the adre-

already said, the lowering of the total carbohydrate at a meal, by the taking

Fourth, by promotion of utilization of carbohydrate between meals the development of acidosis is averted Fifth, frequent feedings of carbohydrate favor its utilization

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but fail in that they do not automatically adjust to the additional load of carbohydrate which a meal demands or the decreased necessity for it induced by exercise, moreover they presuppose a continuous supply of carbohydrate furnished by food or from body storage Only under such circumstances would the long effective PZI act at the best advantage The Toronto workers recognized this situation when RI was introduced and, to

would act only in the presence of hyperglycemia

Test for Glucose in the Urine and Blood.—The more important a diabetic conceives himself to be, the more frequently will he examine his urine or have his urine examined for the presence of sugar If sugar is found, barring

... discloses at which period in the twenty-four hours the diabetes is least controlled, and then one can rectify it by the use of diet, insulin, and exercise
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[36] Bertram Loc cit, p 144

NPH Lente or globin insulin is prescribed. Perhaps a mile walk one, two or three times a day will solve the situation, which one should remember is always solvable. If all tests show sugar, the total diet and carbohydrate usually need reduction.

Testing the urine 4 times daily at the beginning of treatment—namely, on rising and retiring, before the noon and evening meals—is most desirable to demonstrate to the patient how his diabetes is behaving. Frequent testing one or more times daily for life is encouraged. Particularly should the patient be told not to confine his testing to the specimen voided on rising and for two reasons; (1) that it may contain sugar secreted into the bladder many hours before, whereas a freshly secreted and voided specimen half an hour later would be sugar free, showing good control of the diabetes; (2) the rising specimen may be sugar free, due to the going without food all night, but after a meal a specimen of urine would show the presence of sugar.

Occasionally, a 24 hour specimen of urine should be collected and examined so as to determine whether continuously sugar free or to learn the quantity of sugar in the urine for comparison with the carbohydrate in the diet

[illegible] se excreted should [illegible] all, none, and with [illegible] *children, we would* fight to prevent a loss of any sugar in the early months of the disease and would never capitulate to any amount which was more than 10 grams in the twenty-four hours We believe that it is because of such treatment that we have Quarter Century Victory Medal cases, page 236, who are free from degenerative stigmata after twenty-five years of the disease Especially should one be sugar-free at home when the danger from a reaction is less The aim should be to keep the percentage of sugar in the *blood* normal before and after meals, but exceptions will arise in cases with infections, hyperthyroidism, pituitary involvement, and upon occasion in nephritis, heart disease, hypertension, arteriosclerosis, cancer of the pancreas, and almost always for the first few days following operations During pregnancy a renal glycosuric element enters into the picture and glycosuria is out of proportion to the glycemia, thus necessitating repeated small doses of supplementary insulin before the noon and night meals and even upon retiring

To lessen the necessity for blood sugar tests, the patient may empty the bladder and after an interval of half an hour void a second specimen. The *examination of this will far more closely match the per cent of sugar in the* blood than the first specimen, which actually represents the average of *sugar in the urine secreted during the preceding several hours.*

Frequent testing of the urine is necessary for control of diabetes year in and year out One patient, who earned a fabulous salary and filled many key positions, carried home tiny bottles with teaspoonful specimens and had his nurse test six specimens of his urine daily In a quarter century he never had one insulin reaction, and he took about 85 units of insulin in twenty-four hours, because along with testing he combined intelligence, hers and his, in the use of *diet, exercise and insulin* At the beginning of

his thirty-one years of diabetes he decided that he would control his diabetes rather than let diabetes control him, and he succeeded. He could not afford to have a reaction when presiding at corporation or bank meetings.

Large Doses of Insulin Daily Seldom Necessary.—Are 80 units of insulin daily often necessary? Dr. M. C. Balodimos[27] reviewed the records of one hundred recent consecutive patients of the Clinic who, when first coming to us, had been taking for some time a total daily dose of 80 units or more of insulin. The cause for this high insulin requirement was evaluated. Pregnant women in whom the requirement during the last months of pregnancy is known to increase markedly were excluded from this study. The high dosage in 36 patients (36 per cent) was due to their illness *per se*, insulin resistance, acute infection or gangrene, hyperthyroidism, etc. The insulin requirement in these 36 cases remained the same or even rose in the Hospital. Only with the patients in whom the underlying condition could be eliminated did the insulin dose come down. The only cause for the high insulin requirement in 45 patients, however, (45 per cent) was excessive food intake, a more or less "free" diet, accompanied by an attempt to cover

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insulin daily (range from 80–160). Most of them had frequent hypo-

insulin dose, which in some patients actually happened.

Insulin Syringes and Administration of Insulin.—The less the number of types of insulin, the less the number of strengths of insulin, and the less the variety of syringes for its injection, the safer the life of the patient will be. Diabetic coma and insulin reactions will be far less frequent. "Lawyer, doctor, beggar man, thief " or clergyman—all become confused with the different strengths of insulin or types of syringes. At the start of treatment instructions must be simple, thorough, and during its long course often repeated. First, make clear to the patient that insulin

patient measure out in his own syringe and a different syringe a given dose of insulin using water from vials labelled with different theoretical strengths

[27] Balodimos: The Completed Study, to be published.

of insulin—40 and 80 units per cubic centimeter, but be sure the bottles used for purposes of instruction are plainly marked by labels so that no one will mistake them for bottles filled with insulin Practice only will make the use of insulin safe. Urge the patient to bring to the visit his insulin bottle and syringe. The simplest syringe, I believe, is the one which holds one cc. and this is divided into tenths, then the number of units in insulin of any strength can be readily recognized

Regular or crystalline insulin will maintain its potency for many months even at room temperature The long-acting and intermediate insulins are quite stable, but less so than clear varieties. Consequently, it is best to teach patients to keep their reserve supply in the refrigerator, allowing the bottle in current use to remain at room temperature. On the other hand,

ber of units taken, depending, of course, upon the day-by-day urine tests for sugar Insulin should not be used if it has been frozen.

The ideal method of sterilizing the insulin syringe and needle is by boiling Lay needle, syringe and plunger separately on gauze in a small dish, cover with cold water, bring to boiling and continue 5 minutes Pour off water and assemble the parts of the syringe being careful to avoid touching more than the ends of the syringe and plunger and the butt of the needle. Patients who are away from home may find it difficult or impossible to sterilize their equipment by boiling For these, sterilization by alcohol (70 per cent by volume, isopropyl alcohol preferably), is necessary. Various traveling kits are on the market to meet this situation Because of the time taken in water sterilization many patients use alcohol even at home If this is done, a strong test-tube or 4 ounce bottle can be used, this should be sterilized by boiling at least once a week and the alcohol changed When removing the syringe and needle from the alcohol all traces of alcohol should be blown out by motion of the plunger This is important because the alcohol may alter the insulin and besides may lead to irritation when introduced beneath the skin. Sterilization by alcohol must always be regarded as second best, and patients should be encouraged to sterilize by boiling when possible.

Lipodystrophy (Insulin Atrophies and Hypertrophies) —See page 525

Exercise.—Exercise is of great help in the treatment of diabetes It

treatment of the diabetic always takes advantage of exercise whether the patient is in the hospital or at home However, if the blood-sugar lowering properties of insulin and *unusual* exercise are to be combined, one must be

ries required must come almost exclusively from fat and thus fail to be burned and lead to ketonuria. Exercise is so valuable that it should be looked upon as a *duty* and not simply taken up for sport. It should be

doubtedly correlated with the fact that when, at the time of the exercise, the diabetic is deficient in insulin, muscular activity causes a rise and not a

allowance of a patient when he is discharged. Patients receiving the long-acting insulins may require more carbohydrate in repeated feedings to

in the afternoon, but when he has a chance to play golf, 14 in the morning and 10 in the afternoon keep him sugar-free." This patient, Case 2419 developed diabetes at the age of 14.6 years in 1920, he is now in 1958 happily married and has three children. He is our first Quarter Century Victory Medal case, height 72¾ inches, weight 154 pounds undressed, 70 kilograms, and most active in business. His recent diet is approximately carbohydrate 175 grams, protein 100 grams, fat 100 grams, and protamine zinc insulin 70-80 units varying with activity. As a matter of fact, he

diabetic must learn how to use the two blades.

[21] Allen, Stillman and Fitz. P. 468, Loc cit, p. 99.
[22] Marble and Smith. Arch Int Med, 58, 577, 1936.

Exercise for the bedridden as well as the ambulatory patient is essential. The muscles live on sugar and exercise helps them to utilize it. Our hospital cases suffer from lack of exercise. We need a gymnasium for them to supplement our School Room, Dentist's Office, and "Beauty Parlor for Diabetic Feet." Lack of exercise in hospitals makes a diabetic appear worse than he really is. The disarrangement of a patient's routine when transferred to a hospital often makes it extremely difficult to determine his true state. Even before the discovery of insulin the value of exercise was appreciated by one of my wisest diabetics. Case 352, Major W., wrote: "First, it is very hard to start the exercise, and the less one feels inclined to start the more one needs it. Second, it is neither necessary nor desirable that it should be violent. I found a quiet ride of an hour, walking or jogging after taking something on the stomach, started up my old metabolism for the whole day. If I rode hard I got tired out." Various patients on mountain hikes have tolerated unusual quantities of carbohydrate. I was always impressed in former days as was also Bouchardat a 100 years ago with the better results frequently obtained by ambulatory as compared with hospital treatment, provided the same degree of attention was given to the details of the diet and hygiene of the patient. This explains why vacations in the country are so useful. Diabetic children at camp in the summer need less insulin than when at school in the winter. The patient crippled with

required for it must come almost wholly from fat which the patient cannot

helpful must always be supported by insulin endogenous, or exogenous.

Believing so strongly in exercise we are introducing calisthenics in the Hospital Teaching Clinic. The patients do not have time for sufficient exercise but we are trying to encourage all to carry out exercise at home if they fail to get enough in their daily routine.

One evening recently the patients took calisthenics for 40 minutes and it was surprising how many of them showed a reaction. A few days later we repeated the calisthenics but then gave 10 grams of carbohydrate to those with a blood sugar of 60 mg. and 5 grams to those with a blood sugar a little higher and they were free from reactions.

In "Insulin und Insulintherapie" there is this story by Professor Meythaler[39] of Nurnberg. He writes: "I have a severe diabetic who is a postman and daily needs about 100 units of insulin. He rides about 25 kilometers on his bicycle for his route. On account of the danger of hypoglycemia, before he starts out in the morning he sticks his head out the window and if the wind is blowing against him then he lowers the insulin 20 units."

Upon Monday morning, July 23, 1956, there arrived at the 8 o'clock conference in the Joslin Auditorium a patient fresh and smiling, who had

[39] Meythaler. *In*, Stich, Maske *et al.* Insulin und Insulintherapie, München und Berlin, Urban und Schwarzenberg, p. 96, 1956.

just completed a dogtrot of three to four miles from the Parker House in downtown Boston, where the Parker House Rolls originated He was Dr Frederick M. Allen's patient He said that daily he averaged to run 2½ to 4½ miles at the rate of 5 miles an hour and sometimes even ran a total of 10 miles This he had done for many years. In fact, in the 11 days before his visit he had run 83 miles Upon questioning, it appeared (1) that he had diabetes for 26 years; (2) that Dr. Allen had been his sole physician; (3) that he had seen him every 3 months, (4) that he had strictly adhered to the diet and medication with insulin and exercise prescribed. This

His urine showed no sugar or al-

("true glucose"). The non-protein

137 mg. The *x*-ray of the chest

was expected to live if he did not have diabetes

Until I see a patient 85 years old, with 26 years' duration of diabetes who has been treated by loose dietetic measures without an effort to keep the urine sugar free and the blood sugar normal and yet is in as good condition as Dr Allen's patient, I shall continue to be an advocate of close control of diabetes

The Return Visit —If diabetic patients were seen by their physicians every

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diabetics in this country would increase five to ten years It is advantageous at each visit to record the age of the patient and the duration of the diabetes, recheck the presence or absence of heredity and of normal or abnormal weight, because thus one gains a quick perspective of the case

attention is given to the blood pressure and a decision as to the advisability of an ECG, which is always so much appreciated in retrospect if coronary disease supervenes Naturally, one is concerned about the presence of albumin, and any sign of an urinary tract infection (pyelonephritis), even if the blood pressure and NPN are normal and symptoms lacking Coronary

the peculiar behavior of the patient.

The attitude of the doctor toward the patient at the visit should be to impart what new has developed in diabetes since the last visit and to explain what can be done to help the patient control the disease better. Diabetics are bright and they expect to learn of some new and hopeful discovery whenever they come to a doctor's office so that they can immediately profit by it. Why else should they come? Boulin[30a] advises tests for (1) glycosuria and hyperglycemia; (2) ketonuria and ketonemia, and *abnormal* acid base balance; (3) azotemia, (4) hypercholesterolemia.

It is not as routine now as at the turn of the century to count the calories and record carbohydrate, protein and fat, but it is just as useful in the practical treatment of a case, for both the doctor and the diabetic to do so. A calorie is a calorie exactly as it was in the Naunyn Era, and if it is lost in the urine it must be subtracted from the calories of the diet to learn the net calor

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needless protein metabolized and the fat wasted in the formation of ketone bodies. So, too, lost calories in the form of ketone bodies in acidosis are avoidable. Not so formerly. Case 344 excreted 25 to 50 grams β-oxybutyric acid daily for weeks, representing about 5 calories per gram if allowance is also made for other ketone bodies. Now as always it has been the diet of the untreated diabetic which is expensive.

The Fat Diabetic. – It is most exceptional for any individual to acquire diabetes who is ten pounds underweight. At every interview with a diabetic the physician should have a weight card in his pocket and another for the patient ... visits it should be conspicuo

Successful ... It is accomplished if th ... ifically to omit

then each day keep eating less than the day before until it does. So simple as such a regimen appears, it is difficult to carry out unless one has the cooperation of all concerned in the preparation of the food. The thought occurs that if Cantani's methods of putting the patient in a private room with the key turned in the lock could be utilized, success would be the rule. It is far easier to keep the carbohydrate rather than the fat low in the diet. To encourage the adoption of a low calorie diet requires all the art and wile

succeed. Frankly, to lose weight one ...

[30a]Boulin. Traitement Diabète Sucré, Paris, G. Doin et Cie, Bibliothèque de Therapeutique Médicale, No. 15, 1956.

But I must acknowledge that there are many emotional factors which play an important part in etiology, prophylaxis and treatment Dr Hilde Bruch[306b] sympathetically discusses them in her readable book "The Importance of Obesity " In addition she brings up-to-date the importance of the growth hormone and this offers an explanation which forces the doctor to acknowledge that the patient is not 100 per cent blameworthy The 12 pound baby and the eventual diabetic mother soften our attitude toward the fat patient

Insulin stimulates the appetite and the less used the better Perhaps one of the reasons some patients claim they feel better after orinase than insulin is that this stimulating action is absent More frequently than not, however, one is apt to give it promptly so as to overcome annoying symptoms and to keep the patient under closer observation. As to the caloric value of the diet, there is little to be said It should be reduced until the urine is sugar free and weight falls The Benedict test and the scales are the most reliable guides

If a patient loses 1 pound a week for the first 12 pounds, that is usually [illegible]

Fortunately, it is seldom necessary to lower the protein below 1 gram per kilogram

Weight reduction by the free use of fat and protein with reduction of carbohydrate is not applicable to diabetics because of the danger of acidosis. Seldom would one wish a diabetic's carbohydrate to fall below 150 grams because the caloric needs will force an excessive consumption of body fat [illegible]

if you will reduce your diet by 1500 calories you will lose a pound, but it is approximately so See page 263.

A fat person should real[illegible]
relative amount of calori[illegible]
tablespoonfuls (8 teaspoo[illegible]
calories One large slice [illegible]
egg has 78, an ounce of lean meat, about 70, an ounce of bacon, 155, American cheese, 122, butter 225 calories Contrast the above with 4 large portions of the 3 and 6 per cent vegetables which would contain only about 104 calories Milk has 600 to 700 calories per quart, and heavy cream three times as many

[306b]Bruch The Importance of Obesity, New York, W W Norton Co, 438 pp 1957

very, very lean meat or fish with liberal quantities of the bulky vegetables

If a person is in doubt about his diet bringing a reduction in weight, he should simply write down what he has eaten and then the next day eat a little less. Cut out some one thing and see what happens, and if that does not do the trick, the next day he should eat still less until he finds out how *much he must reduce it.*

Some people think they don't eat much of anything. It is a good plan

A police lieutenant once weighed 275 pounds and was 6 feet, 3 inches tall. Upon October 21, 1955, he weighed 250 pounds and I asked him to lose weight. By July 17, 1956, his weight was 218 pounds If he could reduce weight others can. It is simply a question as to whether a patient wants to lose weight and has the backbone to do it.

Appetite Lowering Drugs.—They are a crutch—but I confess that they are often useful

appetite So far as I am aware such drugs are harmless, but I have had little experience with them

Brittle Diabetics.—"Brittle diabetics," a term coined by Woodyatt, included those diabetics who exhibited wide variations in glycosuria and glycemia without obvious causes such as variations in the composition and absorption of the diet, exercise, insulin, infections or alterations in the activity of the pituitary, thyroid, adrenal or liver The more accurately and critically the diabetic is studied, the less frequently such cases are encountered They are, if anything, even less frequent than the two per cent observed by Haunz[31] among 310 diabetics during a period of two years. Other recent references are Colwell,[32] Lamar,[33] Baker and Colwell [34] When

tients that if they found a food produced glycosuria by their own tests of their urine after eating it that it contained too much carbohydrate for them, the explanation of most brittle diabetics was solved. The term "brittle diabetics" like that of acute fulminating diabetes will probably gradually drop out of the literature

I welcome the problem of a so-called "brittle" diabetic because often they are extremely keen, able, hard-working people, who are driving them-

[31] Haunz Jour Am Med Assn, *142*, 168, 1950
[32] Colwell Penn Med Jour, *52*, 1638, 1949
[34] Baker and Colwell Proc Am Diabetes Assn, *8*, 39, 1948
[33] Lamar: Jour Am Med Assn, *142*, 1350, 1950

selves to the limit and are high-strung and tired out. They know much about diabetes but not quite enough. To help them one must secure intimate cooperation, a willingness to learn the truth and then teach them diabetes

to drop exercise out entirely and even prescribe bed rest for a few days until one learns what diet and insulin are necessary to control the disease

To determine the diet and insulin, it must be taken for granted that the meals will always be on time, spread out over many hours, preferably from 7 A.M. to 7 P.M., with 1 to 2 lunches in the forenoon, afternoon and on retiring When the diet is arranged then the insulin can be adjusted to it.

Scrupulous accuracy in computing the diet and uniformity in its absorption are far more difficult to attain today than formerly. Diets are now

patients are no longer bedridden but are active and the exercise more variable Insulin greatly complicates the picture, because of errors in its measurement, due to different strengths and varieties, technique of administration, absorption because of faulty injection in one site rather than in separate sites each day of the month, and especially by injection into areas of lipodystrophy (fat hypertrophies and atrophies)

Tendencies to brittleness may be expected particularly in the young, the thin, the small, the active, emotionally or otherwise, the uncooperative patient or the discouraged patient who has become careless and often thoughtlessly breaks regulations

Children, severe and thin diabetics have a low storage capacity for glycogen Variations, therefore, in total food, carbohydrate, exercise and insulin lead to a more prompt response in the blood sugar, because the glycogen reserve is so low Might it not often be 50 rather than 300 grams? The total fasting sugar in the blood of an adult weighing 70 kilograms is less than 7 grams and in a child of 35 kilograms, 3.5 grams or the equivalent of a small lump of sugar The wonder is that the carbohydrate stored as glycogen and sugar in health and especially in diabetes can be so well controlled, especially when dependent upon an artificial supply of insulin Furthermore, as a rule only about 10 grams of carbohydrate are oxidized

Insulin will be required at least twice a day, preferably NPH before breakfast and the evening meal, with additions to it of crystalline insulin

strikes, just as Sippy taught his ulcer patients to take their milk and cream at short intervals.

Easily, quantities of food can be increased if exercise is increased. After the patient gains confidence, the administration of diet and insulin may be simplified. All agree that in such cases the three meals and three lunches should be spread over at least 12 hours in the 24, and one author even suggests that six injections of crystalline insulin be employed. Generally, two injections of NPH insulin with or without added crystalline insulin will suffice, along with careful adjustment of diet to the four daily tests of the urine.

Dr. Frederick M. Allen[34] has emphasized admirably, the two principles in the management of patients of this type. He writes: "First, prevention of hypoglycemia depends chiefly on frequency of carbohydrate administration; therefore, most severe cases require nourishment between meals. Second, the function of carbohydrate is not to neutralize insulin but to fill up the blood sugar. This is best illustrated by the fact that a reaction resulting from a single injection of 500 units of plain insulin is arrested in the rat by injection of about half a gram of glucose, in the dog by ten or fifteen grams, and in man by about twenty grams. The injection must [illegible] sugar at [illegible] ordinary [illegible] or three hou[illegible] enot[illegible] the [illegible] mea[illegible] no more than the eating of a few raisins or salted peanuts at a specified time. Sugar is of course carried routinely by all such patients as a safeguard against rare needs, arising for example from extra exercise."

Often, I tell patients to take 3 to 5 grams of carbohydrate (a saltine or Uneeda biscuit) between meals when the clock strikes, on the hour at 8, 9, 10, 11 A.M., 12 noon, 2, 3, 4, 5, P.M. and midnight. Longer-lasting results may be had from eating a small (30 gm.) homemade low-carbohydrate doughnut.

With a thorough understanding of the action of diet, exercise and insulin and a hundred per cent desire to adhere to the fundamental rules such patients can get on well, but woe to the inexperienced doctor who has to treat them. Intelligence, honesty and cooperation will win the battle, but it *demands a careful study of all details of life both by the doctor and patient.*

Alcohol In no disease would the employment of alcohol appear to be more useful or more justifiable, but I very rarely give it to diabetics, because of (1) the pathetic cases, relatively few I acknowledge, of alcoholic neuritis which I have seen among diabetics, (2) the liability of a patient [illegible]

[34] Allen. Diabetes Mellitus, In Cyclopedia of Med., Surg. and Specialties Philadelphia, Davis, Chap. 4, p. 505, 1953.

age who used it in excess and (5) my personal disapproval. It breaks my heart to see free cocktails advertised as a lure to secure attendance at a scientific gathering Think of the sums spent upon alcohol and tobacco and what even a portion of the same could accomplish if diverted to food,

(6) there are no vitamins in alcohol.

A diabetic, taking insulin, should never venture on the street with an alcoholic breath. According to Newman and Cutting[36] insulin accelerates the metabolism of ethyl alcohol 50 per cent in therapeutic doses in man Alcohol is not convertible directly into glucose or fatty acids, i.e, neither ketogenic nor anti-ketogenic Higgins, Peabody, and Fitz[37] from tests upon themselves when upon a carbohydrate-free diet found that alcohol did not show any anti-ketogenic action

Few of our cases have taken alcohol and still fewer take it now than in

is limited not only in respect to carbohydrate (preformed or potential) but also in respect to total calories as such They found that alcohol, which is clearly recognized as not convertible into sugar or acetone in the body produces a return of glycosuria and other symptoms when added to the diabetic diet in quantities exceeding caloric tolerance

Tobacco.—I cannot prove or say that cigarettes favor neuritis, retinitis or cancer of the lung, but I advise diabetics to leave cigarettes alone As for other types of tobacco I am less positive This whole question of tobacco is being investigated with great care. Therefore, I refer to the study, "Smoking and Death Rates—Report on Forty-four Months of Follow-up of 187,783 men "[39]

THE METABOISM OF THE DIABETIC

Between 1908 and 1920 I was associated ...
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[36] Newman and Cutting Jour Clin Invest, 14, 915, 1935
[37] Higgins, Peabody and Fitz Jour Med Res, 34 263 1916

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employed in large doses and continued for periods of months Fat was given

of treatment based upon a reduced calorie intake

The results of our studies of these 118 diabetics showed (1) that not one of the number had lost all power of utilizing carbohydrate and therefore by implication in all diabetics there was always a residue of functioning islands of Langerhans, an opinion also shared by von Noorden based on his experience in the care of 30,000 diabetics; (2) that with overfeeding in the Naunyn Era with low carbohydrate and high fat, and the resulting acidosis the metabolism was increased +13 per cent, the six with the highest metabolism ranging between +26 and +33 per cent, and the respiratory quotient was 0 70, nearly that of fat, (3) that with the advent of undernutrition in the All

−7 per cent on the

being −40 per cen ,

became 0 84 and with experimental carbohydrate feeding the respiratory quotient rose above 1 0, which was interpreted as a conversion of carbohydrate to fat The conclusion of the study of the metabolism of these diabetic patients indicated that it was normal but varied greatly according to whether the doctor prescribed the caloric value of the diet to be high or low The degree of severity was due to the doctor rather than to the disease.

[40a] Hodgson Jour Am Med Assn, *67*, 1187, 1911
[40b] *Guelpa Brit Med Jour, 2, 1050, 1910*
[41] Allen Jour Am Med Assn, *63*, 939, 1914, See also in earlier literature

Chapter 10

ORAL HYPOGLYCEMIC AGENTS

By Alexander Marble, M.D. and Leo P. Krall, M.D.

A. EARLY OBSERVATIONS

[illegible]

observed that in certain diabetic patients glycosuria and acetonuria cleared with the use of Synthalin The peak action of the drug did not occur until after 24 hours following administration Large doses caused [illegible]

the advent in 1921, of insulin with its obvious physiological advantages lessened greatly the interest in Synthalin, as late as 1926 Minkowski[7] stated "It is a momentous fact that the practical results exceeded all hopes [illegible]
could help [illegible]
was a spa[illegible]
papers I[illegible]
Synthalin were diminished by the administration of decholin In 1928, Frank and Wagner[10] reported clinical success with no toxic effects and announced a Neosynthalin with 12 methyl groups However, some disquieting reports continued to appear Hornung[11] thought that the side [illegible]

1916

24, 341, 1921
926.
52, 2067, 1926

Bertram[13,18] emphasized the toxic effects of Synthalin and gave references to cases of liver damage reported in the literature of the time.

Further reports of toxicity coupled with the physiological soundness of insulin produced a further decrease in interest in Synthalin causing it to drop out of sight until comparatively recent years when its use was revived

an aqueous calves' liver preparation orally caused a definite decrease in blood sugar levels. Although they speculated that these extracts might

ported that extracts of roots of the Devil's club (*Fatsia horrida*), a wild plant growing along the coast of British Columbia, possess hypoglycemic properties. Somewhat similar findings were obtained by MacDonald and Wishcki[22] who made extracts of large quantities of raw cabbage. Lewis[23] was unable to confirm this. Reports have appeared regarding the hypoglycemic action and possible therapeutic value of extracts from certain other plants and fungi: (1) "cundeamor," made from Momordica charantia and investigated by Rivera[24] in Pureto Rico, (2) "amellin," isolated from *Scoparia dulcis* Linn. and studied by Nath and associates[25] in India; (3) "sumach" or staghorn shrub (*Rhus typhina*);[26] *Pterocarpus marsupium* and Eugenia jambolana[27], *Aspergillus niger*,[28] and Fungi imperfecti from avacado leaves.[29] Various plants and plant extracts throughout the world over many years of time have been accepted by local inhabitants as possessing anti-diabetic properties. However, these have been ineffective when

[13] Szczeklik: Wien. klin. Wchnschr., *40*, 1075, 1927.
Med., *14*, 690, 1929.
l and Exper. Therap., *36*, 61, 1929.
58, 76, 1927.
1952.
02, 1953.
Assn., *94*, 1811, 1930.
ssn. Jour., *39*, 32, 1938.
l., *94*, 219, 1938.
950.
911. Ibid., *114*, 72, 1912.
Med., *3*, 1914, in 5 parts: I, pp. 55-62
130, V, pp. 147-156. See also Nath and
ed., *75*, 326, 1950.
ssn., *27*, 358, 1956.
1951.
85, 1957.

subjected to rigid tests. Nash *et al*[30] found no effect in alloxan diabetic rats and mice from *Tecoma stans* despite its use in Mexican folk medicine In interpreting results obtained with these and similar preparations, it is necessary to keep in mind that a substance may lower the blood sugar without being able to correct the faulty metabolism of diabetes

B THE ARYLSULFONYLUREA COMPOUNDS: GENERAL CONSIDERATIONS

Historical Background.—At the time of the development and intro-

associates working at Montpellier, France, with sulfa-isopropyl-thiadiazol (2254 RP) They, together with Loubatières and co-workers[33] presented their results at the 43rd Congress of French-speaking Neurologists in October, 1942 Somewhat later, Chen, Anderson and Maze[34] in the

N[1]-n-butylcarbamid), noted that subjects developed fatigue, sweating, hunger and tremor reminiscent of the signs and symptoms of hypoglycemia due to insulin. Consequently, the blood sugar was determined and found indeed to be low Use of the drug in diabetic patients met with success in many The work was extended to include hundreds and eventually thousands of patients in Germany[36] and from this country the clinical trial of the arylsulfonylureas was extended all over the world

Carbutamide —German clinicians quickly found the BZ 55 was ef-

Although it was found to be a potent hypoglycemic agent in responsive

nd Med , *8*, 350, 1950
21–22, 441, 1942

Med , *63*, 483, 1946.

individuals, the incidence of side effects was considered too high for general use. Of 7193 patients who had received the drug, 5.4 per cent had toxic effects consisting chiefly of allergic skin responses, nausea, vomiting, abdominal distress, leucopenia, agranulocytosis and liver damage with jaundice.[37] There were eight deaths which seemed quite likely to have been due

withdrawn

rbutamide

For some

reason as yet unexplained, fewer toxic effects have been reported by physicians outside the United States.

Tolbutamide.—Not long after the introduction of BZ 55 in Germany, a second sulfonylurea compound was made available for clinical trial. As may be seen from Figure 17, this new agent (designated as D-860 in Germany) differs from BZ 55 only in the substitution of a methyl for an amino group in the para position on the benzene ring. This substitution produces three effects: (*a*) The compound is somewhat less active as a hypoglycemic agent (*b*) It is not antibacterial. (*c*) It is less toxic and produces fewer side effects.

D-860 was designated in the United States as tolbutamide and has been known by the trade name of Orinase* given it by the Upjohn Company. Tolbutamide was introduced in the United States shortly after carbutamide and has been studied extensively both in the laboratory and clinic. In general, the effect of tolbutamide on the blood sugar is much the same as that of carbutamide although, as mentioned above, is somewhat less active in this respect The types of patients with which tolbutamide is effective are the same as with its companion product.

Chlorpropamide.—Late in 1957 there was introduced for clinical trial in the United States another sulfonylurea compound designated as chlorpropamide (1-propyl-3-p-chlorobenzenesulfonylurea) and given the trade name of Diabinese by Chas Pfizer and Co, Inc As is evident from Figure 17, it is a propyl rather than a butyl compound and has a chlorine ion in the para position on the benzene ring It is a potent hypoglycemic agent which lowers the blood sugar in the same type of subjects and under the same conditions as carbutamide and tolbutamide The effective dose is smaller than that of tolbutamide, ranging from 0.25 to 0.5 gm. daily. Absorption of the drug from the gastro-intestinal tract is prompt but its rate of disappearance from the blood and its excretion in the urine are much slow

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(N-3-amino-4-methylbenzenesulfonyl'-N-cyclohexylurea) has been initiated by Eli Lilly and Company Like chlorpropamide, its effective dose is small, 50 to 300 mg daily So far no significant untoward effects have been reported

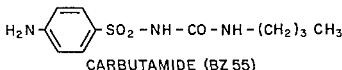
[37] Kirtley Diabetes, *6*, 72, 1957

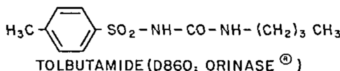
C TOLBUTAMIDE (ORINASE)®

Under the trade name of Orinase®, on June 10, 1957, tolbutamide was made available in the United States for general use on a physician's prescription A detailed description of the drug was published in the July 20, 1957, issue of the Journal of the American Medical Association by the Council on Pharmacy and Chemistry.

Our experience at the Joslin Clinic began in February, 1956. Every attempt has been made to follow patients carefully to ascertain the results of treatment and to recognize and record any untoward or toxic effects

Selection of Patients for Tolbutamide —Since tolbutamide is effective only in certain middle-aged and elderly diabetic patients, it was necessary early





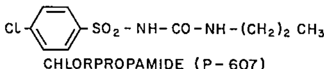


FIG 17 —Formulas of three sulfonylurea compounds (The Chas Pfizer Co name for Chlorpropamide is "Diabinese")

in its use to develop methods by which patients could be selected properly Methods which have been proposed are the following

(*a*) Clinical trial
(*b*) Evaluation of type of diabetes with particular reference to ketosis
(*c*) Sulfonylurea response test

(*a*) *Clinical Trial* —The most direct method of testing is simply to start

dosage of 1 gm. daily for a prolonged period. It will be found that with responsive patients usually 1 gm. daily will suffice and at times the dose may be as low as 0.5 gm. daily. If the patient has previously been on insulin, the attempted transition to tolbutamide must be watched closely lest control of the diabetes be lost and acidosis supervene. It is best to have such patients in the hospital during the attempted shift to tolbutamide. In any case, the amount of insulin may be reduced by 10 to 25 per cent every second or third day until it can be ascertained as to whether tolbutamide will be effective. If tolbutamide is only partly effective and it appears that insulin will need to be continued, even if at a lower dosage, then it is probably best to return to the full dose of insulin since combined insulin-tolbutamide treatment would appear to offer little or no advantage.

(*b*) *Tendency to Ketosis.*—Duncan, Lee and Young[28] have proposed that patients be selected for tolbutamide depending upon the ease with which they develop ketosis. Consequently, they suggest withdrawal of insulin in hospitalized patients and determination of the number of hours required [illegible] those [illegible] 's con- [illegible] hin 24 hours, oral treatment may be attempted with reasonable assurance of success. The chief objections to this manner of selection of patients are the need for hospitalization, the temporary upset in the diabetic condition due to withdrawal of insulin and, in inexperienced hands, the possible hazard of ketoacidosis to the patient.

(*c*) *Sulfonylurea Response Test.*—Since the beginning of our experience with sulfonylurea compounds at the Joslin Clinic, we have employed a response test which has been most helpful. The directions are as follows:

(1) In patients whose insulin requirement is small, say 12 units or less daily, omit insulin entirely for the two days prior to the test day. In [illegible] tinue insulin for the two days [illegible] zinc, NPH, lente, or globin, [illegible] will be no carry-over of insulin effect on the test day.

(2) On the day of the test, omit insulin and breakfast.

(3) Obtain blood (fasting) for sugar determination.

(4) Give 3 gm. of tolbutamide by mouth.

(5) Obtain blood for determination of sugar content 4 hours later.

After the above has been accomplished, the test is terminated and food may be given. When carried out as an office or out-patient procedure, the patient should be asked to wait for an hour or so until the blood sugar values have been reported. If the response to tolbutamide has been satisfactory, the patient may be asked to begin on the following day with a maintenance dose of 1.0 gm. daily before breakfast. If the results of the test have been unsatisfactory, an appropriate dose of insulin should be given before the [illegible] -patient clinic. In this way [illegible] be avoided in patients who

[28] Duncan, Lee and Young: Ann. New York Acad. Sci., 71, 233, 1957.

[illegible]

values obtained by the Somogyi-Nelson technique, we have insisted that the blood sugar fall to 110 mg. or below in order to be considered a good test If such takes place, it may be predicted with a reasonable degree of accuracy that the patient will respond satisfactorily to tolbutamide on maintenance doses over days and weeks of time

It is true that with some individuals the maximum effect of a single large dose of tolbutamide may not be secured until after 6 or 8 hours Such subjects would be missed in the 4-hour test and, therefore, might not be selected for the oral treatment. However, the number of such patients is not large Although the 4-hour test lacks complete reliability in its prediction, it is probably the most satisfactory and convenient one available and as a screening procedure in the selection of patients it has proved extremely useful

Factors Affecting the Success of Tolbutamide Treatment.—Late in 1957 survey was made of the results of tolbutamide treatment in the Joslin Clinic with patients seen both in the office and at the New England Deaconess Hospital [39] Up to November 10, 1957, 1030 diabetic patients had received tolbutamide In 772 of these, treatment with tolbutamide had actually been begun, other patients in the larger group had had only the single-dose response test Of the 772 patients, treatment had been carried out in 594 persons for 1 to 20 months up until the time of the survey. Of the *selected* group of 772 patients, good control of hyperglycemia and glycosuria was obtained in 407 or 52.6 per cent and fair control in 143 or 18 5 per cent The incidence of failures was as follows: "primary" (*i e*, within the first month of treatment), 136 patients or 17 6 per cent, "secondary" or late failures, 40 patients or 5 2 per cent Nine of the secondary failures were probably due to disregard of diet There were 33 patients or 4 3 per cent with whom the drug had been used for less than one month, 8 patients (1 1 per cent) with whom tolbutamide was stopped because of toxic side effects, and 5 patients (0 6 per cent) with whom the drug was discontinued for non-medical reasons

[illegible]

of relatively much more importance than the age at the time that tolbutamide was given or the duration of diabetes The size of the insulin dose carried much more weight than the duration of time over which insulin had been taken

Untoward Effects —Side effects were low in incidence (1 1 per cent) and in general consisted chiefly of urticaria and minor digestive disturbances No instance of leucopenia or agranulocytosis was encountered Determinations of liver function were carried out with 392 patients over the course of a year [40] The tests included the blood bilirubin, cephalin flocculation,

[39] Mehnert, Camerini-Dávalos and Marble Jour Am Med Assn, *167*, 818, 1958
[40] Mehnert, Camerini-Dávalos and Marble To be published

thymol turbidity and flocculation, bromsulfalein and alkaline phosphatase determinations. In so far as possible serial determinations were made No consistent or important abnormality was found except in the case of the alkaline phosphatase tests. Here, determinations done a month after starting the drug showed in general a slight rise averaging about one Bodansky unit. This higher level was in general maintained but there was no further consistent rise and often a fall. The significance of the alkaline phosphatase behavior is not clear

In one patient with cirrhosis of the liver (case 48575, female, aged 64 years with diabetes of 3 years duration), jaundice lasting two weeks occurred three months after beginning tolbutamide. The relation of jaundice to the drug is uncertain but it is evident in retrospect that the giving of tolbutamide to this patient with hepatosplenomegaly, grossly abnormal *liver function tests and many large and tortuous esophageal varices from* which later massive bleeding took place, was unwise

Mode of Action.—The demonstration that a sulfonamide-related compound can lower the blood sugar was amazing from the start, and continues to be so The attempt to answer questions—why? how? where?—regarding the action of the sulfonylureas has resulted in an extraordinarily large amount of investigative work thoughout the world. This has resulted in the publication of papers so large in number and so varied in content as to defy summary here but many articles are given or referred to in the published accounts of symposia [41–46]

Among the mechanisms of action which have been suggested are the following:

(*a*) Damage to the alpha cells of the pancreas and consequent inhibition *of production of glucagon* [47] One of the first theories proposed, it has been abandoned for lack of evidence

(*b*) Increase of utilization of glucose by peripheral tissues by means of a direct insulin-like action So far the weight of evidence is against this idea The sulfonylureas do not appear to be substitutes for insulin and *in vitro* they do not seem to act on insulin-sensitive tissues to increase glucose uptake or utilization. In the intact animal or man, the presence of a pancreas capable of producing insulin (or possibly in certain animals of an appropriate amount of injected insulin) seems to be essential for the action of the sulfonylurea compounds

(*c*) Inhibition of insulinase or of [illegible] Some data have been presented to suggest that tl[illegible] insulinase[48] but the evidence is not [illegible] be the answer to the problem The sulfonylureas seem not to oppose

[illegible] Effects of Sulfonylureas in Diabetes

[illegible] 7 Reported 1957

[illegible] ds in Experi- [illegible] 7

[illegible], 78, 1955 [illegible] 1957

those who have had diabetes for 4 to 5 years or more.[49] Further evidence suggesting that the sulfonylureas stimulate the pancreas is afforded by the finding of an increase in the insulin-like activity of blood obtained from the pancreatic vein following the giving of these drugs.[50]

carbutamide or tolbutamide there is no rise in respiratory quotient, no increase in the arterial-venous glucose difference and no increase in blood glucose or pyruvate levels following the giving of glucose intravenously and no decrease in serum phosphate following glucose. As a possible explanation it has been suggested that perhaps the quantities of insulin released from the pancreas in response to the sulfonylureas is so small that metabolic effects of the type just mentioned, although present, are so slight as to escape measurement.

(e) Decrease in the rate of release of glucose from the liver by means of inhibition of enzyme systems. This possible mode of action has gained much support from the results of work of various investigators. Although Levine[51] has reported that tolbutamide is effective even in the absence of the liver, it must be admitted that the hepatectomized animal is a most unphysiological preparation from which it is hazardous to draw firm conclusions in the field in question. A major effect of the sulfonylureas would appear to be that of inhibition of hepatic glucose synthesis or release. It may be argued that this action is benign and favorable since one of the features of diabetes is instability of material stored in the liver with excessive formation, and subsequent release into the blood, of glucose from both carbohydrate and non-carbohydrate sources.

In summary, at the present time it appears that the sulfonylurea compounds act both by stimulating the production and/or release of insulin and inhibition of glucose formation in, or release from, the liver. More exact information awaits further study.

[49] Camerini-Dávalos, Marble, White, Belmonte and Sargeant. New England Jour. Med., *256*, 817, 1957.
[50] Pfeiffer. Personal communication. Also, Pfeiffer *et al.* Deut. med. Wchnschr., *82*, 1568, 1957.
[51] Levine and Sobel. Diabetes, *6*, 223, 1955.

D. THE BIGUANIDES

In 1929, Slotta and Tschesche[53] reported the hypoglycemic action of some lower alkyl derivatives of biguanides (also known as formamidinyliminoureas) when give
derivatives result
urea hydrochlori
extensive trial. U
substance, admin
guinea pigs, rats, rabbits, cats and rhesus monkeys. It also reduced and maintained at a normal level the blood sugar of alloxan-diabetic rats, rabbits and monkeys.

Phenethylbiguanide (DBI) is not a sulfonylurea derivative (Figure 18) but is a biguanide, derived from formamidine. It is a white crystalline solid, soluble in water. Other than its hypoglycemic effect, it has no known significant acute pharmacologic action. There are two closely allied analogues: The isoamyl derivative (DBTU) and the normal amyl derivative (DBB). All of these possess hypoglycemic action. DBI is the most hypoglycemic and least well tolerated, while DBTU is best tolerated and least effective in lowering the blood sugar. DBB lies between the other two compounds in both characteristics.

Pomeranze and his group[44] did the first clinical studies and reported that, given orally, DBI produced an improvement in glucose tolerance in patients with severe as well as mild diabetes, suggesting that except for side effects at the larger dose levels, this substance was useful in replacing insulin in certain patients. Krall and Camerini-Dávalos,[46] after an early evaluation of 20 cases, stated that this substance appeared to have definite blood sugar lowering properties although the mechanism of action was not yet known. They also reported annoying side effects which were restricted to the gastrointestinal tract
tion in June, 19
group of 104 p
lowering eff
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sulfonylure
every age,
same meeting, Williams and co-workers[47] presented results relating to the hypoglycemic action of phenethylbiguanide. They confirmed the blood sugar lowering effect and pointed out that under the influence of phenethylbiguanide *in vitro* the isolated rat hemidiaphragm exhibited an increased uptake of glucose with a decreased glycogen content. They suggested that the hypoglycemic effect might be due to an increased anaerobic glycolysis and cited evidence which suggested that there might be a

Chem Ges, *62B*, 1398, 1929
Soc Exper Biol and Med, *95*, 190, 1957
d, 193, 1957
15, 1957
Arch Int Med, *102*, 25, 1958
and Swanson In press

level in about 70 per cent

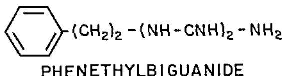


FIG 18 —Formula of phenethylbiguanide (DBI)

TABLE 58 —CONDITIONS OF STUDY AND CRITERIA OF SUCCESS IN PATIENTS RECEIVING BIGUANIDES

1 Patients on a constant diet
2 Those with no insulin previously must show a drop of at least 25 per cent in average blood sugar levels
3 Those previously maintained on insulin must have insulin replaced by DBI and have blood sugar values as good or better
4 In those requiring both insulin and DBI, the insulin dose must be reduced by 50 per cent or more
5

A high incidence of side effects, about 25 per cent, limited exclusively to the gastrointestinal tract, was found These consisted of anorexia, nausea, vomiting and diarrhea, with frequency of occurrence in that order; they

Ungar[60] has reported also the results of a 6-month toxicity study Twenty

of 6 months There were no histological changes in any body organ. Our series of 75 patients receiving the biguanides for one year have shown no

[58] Weller and Macaulay Personal communication
[59] Lanzner personal communication

significant changes in liver function or in blood and urine studies to date. Pomeranze[60] reports no changes after 18 months.

The most significant characteristic appears to be the ability of the biguanides to lower the blood sugar in long-term, unstable and juvenile-type diabetics, although this cannot be accomplished in severe ... t some insulin ...

be ...

Critical Appraisal of the Biguanides.—Any oral hypoglycemic agent must be evaluated by asking ... safe? (3) ...

(1) Ther ... biguanides ... of patients. There seems to be no constant relationship of dose to size or age of subject or to duration of diabetes. The duration of action in therapeutic doses is under 8 hours, necessitating divided doses ...

(2) ... use of t ... of side ... betwee ... the dec ... in the configuration, but also in sp ... however, that there are some ma ... drugs. It must also be remembered that some years passed before Synthalin was proved physiologically undesirable.

(3) The physiological action is the least known aspect of this problem. The mechanism of action is not known. Although muscle (diaphragm *in vitro*) utilizes glucose in the presence of DBI, it has not been shown to convert this to glycogen. While ... humans[62] to show reduced blood s ... can be sustained for long periods ... 1 no effect ...

... isocitric dehydrogenase is inhibi ... oxidized normally via the Kreb ... biguanides utilize carbohydrate through a mechanism foreign to either insulin or the sulfonylureas. While the site of action is not known, it is possibly in the liver enzyme systems.

[60] Pomeranze ...

... 958

... dies related to the Hypoglycemic ...

E FINAL COMMENT

It is too early to make any more than a preliminary evaluation of the place of the sulfonylureas or the biguanides in the management of diabetes At the present time, carbutamide, though withdrawn from clinical trial in the United States is used in other countries Tolbutamide and chlorpropamide, sold on prescription, appear useful in certain middle-aged and elderly patients with mild diabetes Other sulfonylurea compounds of even

TABLE 59 —PRESENT STATUS, ORAL HYPOGLYCEMIC AGENTS*

Substance	Carbutamide (BZ 55)	Tolbutamide (Orinase®)	Phenethylformamidinyliminourea HCl (DBI)
Class	Sulfonylurea	Sulfonylurea	Biguanide
Clinically Studied	In thousands of patients in U S and abroad (4 years)	(3 years)	1000 patients 2 years
Dose	0 5–1 0 Gm	0 5–2 0 Gm	0 05–0 4 Gm
Site of Action	(1) stimulate insulin production (2) oppose liver enzyme action and reduce glucose released in blood		not known possibly in liver enzyme system
Side Effects	reported	relatively few	frequent
Toxic Effects	reported	none reported yet	none reported yet
Effective Blood Sugar Lowering	Middle-aged and elderly patients with mild diabetes		All types in relatively small series thus far
Not Recommended	Juvenile or unstable diabetics, diabetic acidosis, coma, fever infections, during major surgery		Some effects in juveniles and unstable diabetics with small amounts of insulin
Present Status	Withdrawn U S A Still used abroad	Available on prescription	Clinical trials and investigational use

*See text for data regarding chlorpropamide and metahexamide

more recent introduction are in the stage of preliminary trial The biguanides have yet to establish their [illegible] of side effects can be reduced an[illegible] they may be useful in the stabili[illegible] diabetes One thing is certain [illegible] agents in the past few years has stimulated research into the nature of diabetes to an extent not seen since the period just following the discovery of insulin

Chapter 11

HYPOGLYCEMIA DUE TO INSULIN

Alexander Marble, M.D.

A INTRODUCTION

Episodes of hypoglycemia due to insulin constitute one of the major problems in the treatment of diabetes. It is not an indifferent matter for a clergyman, a girl or a boy to be sent to jail upon the supposition that he or she is drunk or to a hospital as an epileptic; for students to fail in a long written or oral examination upon which a rating for the year depends; or for directors of large corporations to develop irritability, garrulousness, tremor or somnolence at an annual meeting of their boards. The fear of an "insulin reaction" is almost worse than the actuality. Moreover, the dangers of a reaction to limb and life, the diabetic's and his companion's, apart from those which injure the reputation, are by no means trifling. The fatalities are few, although probably the unrecorded instances exceed in number those which have appeared in the literature.

It is imperative that diabetic patients avoid frequent insulin reactions. Not only are they inconveniencing and embarrassing to the patient but their occurrence reflects upon the ability of diabetic individuals as a whole to take a normal part in everyday life. Among the disadvantages to the patient is *the fact that hypoglycemia induced by insulin leads to hyperglycemia* because the process of hepatic glycogenolysis set in motion to correct the hypoglycemia overshoots the mark with the result that hyperglycemia results.[1]

Even before the introduction of insulin, hypoglycemia had begun to appear as a serious factor in the treatment of diabetes. In 1921, 3 cases (1831, 1846 and 1883) were reported under the title, "The Critical Period of Hypoglycemia in Undernutrition,"[2] and subsequently a fourth was rescued by Root from impending death by the giving of orange juice.

B SIGNS AND SYMPTOMS

When, following an injection of insulin, an individual develops certain symptoms among which are ... hunger, headache, numbnes... action, double vision and ... reaction. In more severe ...

[1] Somogyi: Proc. Soc. Exp. Biol. and Med., 38, 51, 1938. See also Somogyi, Weichselbaum and Kembrecker: Ibid., 37, 62, 1937.
[2] Joslin: Med. Clin. North America 4, 1723, 1921.

vulsions may occur In patients receiving unmodified insulin, such reactions appear most commonly three or four hours after a meal before which insulin has been given, but may occur in the interval between the administration of the insulin and the taking of food if that interval is unduly

adequate food supply, particularly carbohydrate, either in the diet or as a

or in the muscles, as in progressive muscular dystrophy, will accomplish the same result. Ketonuria may occur in hypoglycemia [84]

When a diabetic child becomes quiet, lacks interest and is unnaturally good or conversely when the child is unnaturally fretful, when an adult diabetic acts ambitionless, depressed and morose, or an elderly man or woman becomes weak and faint, one should suspect that the blood sugar has fallen below normal. If the occasion is some hours after meals, particularly if the patient has had an active period of exercise, and if one learns that he took his usual dose of insulin and in haste ate less than usual, one feels reasonably sure that the suspected diagnosis is correct The surmise changes to certainty if one finds a tremor of the hands with moisture in the palms and a few beads of sweat on the forehead Diabetics in such a condition may respond to questions like an automaton or, quite the reverse,

that sudden decreases of
levels may give rise to
conditions, but none of
us recalls even a situation of this type unless the blood sugar has fallen to at least 100 mg per cent From the very inauguration of treatment with insulin in 1922 we have endeavored to secure blood for the later *determination of its sugar content before administering carbohydrate for a* supposed reaction This policy has certainly lowered the number of sup-

Chapter 11

HYPOGLYCEMIA DUE TO INSULIN

ALEXANDER MARBLE, M.D.

A. INTRODUCTION

EPISODES of hypoglycemia due to insulin constitute one of the major problems in the treatment of diabetes. It is not an indifferent matter for a clergyman, a girl or a boy to be sent to jail upon the supposition that he or she is drunk or to a hospital as an epileptic; for students to fail in a long written or oral examination upon which a rating for the year depends; or for directors of large corporations to develop irritability, garrulousness, tremor or somnolence at an annual meeting of their boards. The fear of an "insulin reaction" is almost worse than the actuality. Moreover, the dangers of a reaction to limb and life, the diabetic's and his companion's, apart from those which injure the reputation, are by no means trifling. The fatalities are few, although probably the unrecorded instances exceed in number those which have appeared in the literature.

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glycemia because the pr[illegible]
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B. SIGNS AND SYMPTOMS

When, following an injection of insulin, an individual develops certain symptoms among which are sweating, nervous instability, tremor, faintness, hunger, headache, numbness or tingling of the tongue or lips, rapid heart action, double vision and unsteady gait, he is said to be having an insulin reaction. In more severe attacks, unconsciousness with or without con-

[1] Somogyi: Proc. Soc. Exp. Biol. and Med., 38, 51, 1938. See also Somogyi, Weichselbaum and Nembrecker: Ibid., 37, 62, 1937.
[2] Joslin: Med. Clin. North America, 4, 1721, 1921.

attacks due to this type of insulin occur usually during the nighttime and [illegible]

the usual hour. Another important feature is that treatment of reactions due to protamine zinc insulin may often require repetition at hourly or half-hourly intervals because of the persistence of the tendency to hypoglycemia. Symptoms following protamine zinc insulin at times consist of headache, usually occipital, and mild nausea, rather than trembling, sweat- [illegible] nature occurring [illegible] onally the nausea [illegible]

those due to regular or crystalline than to protamine zinc insulin.

Reactions Without Warning.—A distressing situation is that of the patient who, usually after 10 or more years of taking insulin, begins to find that reactions occur without warning. Symptoms of severe degree involving the central nervous system appear and are obvious to others but the patient, not having been warned by "adrenalin-like" symptoms,[13] is unaware of the trend of events. He may exhibit abnormal and irrational behavior, act as if an automaton, or lapse into stupor or unconsciousness with or without [illegible]

the amount of physical activity taken daily.

Classification of Signs and Symptoms.—The signs and symptoms of hypoglycemia, particularly relating to the nervous system, can be grouped in three types according as to whether they concern the (*a*) vegetative (sympathetic) nervous system, (*b*) the central nervous system, or (*c*) are psychical.[14,15]

Sympathetic Nervous System.—Belonging in this group are (1) Hunger and faintness. (2) Muscular weakness. Motion of arms and legs, speech and even standing may be difficult. The extremities are as "heavy as lead." Tremor may be pronounced. (3) Sweating. Beads of sweat may appear on the forehead, and the palms, soles and axillæ often become [illegible]

(4) The pulse and blood-pressure vary with the stage of the reaction and the epinephrin response. There may be definite, though almost invariably temporary, changes in the electrocardiogram. (See page 447.) (5) A leukocytosis is not infrequent although one does not see values as

[13] Maddock and Krall: A. M. A. Arch. Int. Med., *91*, 695, 1953.
[14] Wilder: Deutsch. Ztschr. f. Nervenh., *112*, 192, 1929; Klinik und Therapie der Zuckermangelkrankheit, Leipzig, Weidman & Co., 1936.
[15] Falta: P. 118, loc. cit., p. 79.

study of 14 patients who were having frequent "insulin reactions," concluded that when the hyperventilation syndrome occurs in anxious diabetic patients, it can produce symptoms that simulate, and are easily misinterpreted as, true insulin reactions.

Again confusion occurs in patients' minds regarding an insulin reaction when they note the characteristic symptoms and yet find that the urine contains sugar. They do not realize that the glycosuria demonstrated by the Benedict test may represent sugar excreted by the kidneys minutes or hours previously and then retained with the urine in the bladder. In a true reaction a second, freshly passed specimen of urine will be found to be sugar-free provided the bladder was thoroughly emptied at the previous micturition. At such times a therapeutic test of the genuineness of a reaction is prompt recovery following the giving of 5 to 20 grams of carbohydrate.

The severity of an insulin reaction is by no means definitely commensurate with the extent of the hypoglycemia. Sigwald,[6] emphasized this point repeatedly. Particularly in children, blood-sugar levels of 40 mg. per cent may be present without recognizable symptoms. Rabbits kept quietly at rest may exhibit low blood sugar values without symptoms, only to have them appear at the clap of the hand. A diabetic in seemingly good condition jumped off a haymow in company with 30 other diabetics and instantly went into a reaction. With necrosis of the mid-brain Hogler and Zell[7] showed that a lowering of the blood sugar in rabbits might be extreme without bringing on convulsions. Phenobarbital acts similarly. During a severe insulin reaction there may be actually no "true glucose" in the blood;[8] any blood-sugar value of 15 to 25 milligrams per cent obtained by the Folin-Wu or similar method in common use must be regarded as representing almost entirely, if not entirely, non-glucose reducing substances.

Rabinowitch and Peters[9] reported in 1929 the case of a young diabetic who had for six hours a "true" blood sugar of *zero* without symptoms! Maddock and Trimble[10] examined the blood of several patients at hourly intervals for the content of sugar. They were astonished to find how frequently values as low as 50 milligrams per cent occurred with or without symptoms. Everett[11] reported the case of a comatose patient whose blood sugar when first seen was only 10 mg. per 100 cc. but who regained consciousness within an hour after receiving glucose intravenously. Smith's[12] case

Symtoms of Reactions Due to Insulins with Prolonged Action.—

[6] Sigwald. L'Hypoglycemie, Paris, G. Doin et Cie, 1932
[7] Hogler and Zell. Ztschr. f. d. ges. exp. Med., *86*, 158, 1933
[8] Dotti and Hrubetz. Jour. Biol. Chem., *113*, 141, 1936
[9] Rabinowitch and Peters. Am. Jour. Med. Sci., *178*, 29, 1929
[10] Maddock and Trimble. Jour. Am. Med. Assn., *91*, 616, 1928
[11] Everett. Canad. Med. Assn. Jour., *61*, 166, 1949
[12] Smith. Boston Med. and Surg. Jour., *195*, 663, 1926

unconscious state by his family in the morning when he does not arise at the usual hour. Another important feature is that treatment of reactions due to protamine zinc insulin may often require repetition at hourly or half-hourly intervals because of the persistence of the tendency to hypo-

may be marked and vomiting may occur

Patients experiencing hypoglycemia from NPH, lente or globin insulin taken before breakfast are likely to experience such in the middle or latter part of the afternoon. The symptoms are apt to resemble more nearly those due to regular or crystalline than to protamine zinc insulin.

Reactions Without Warning.—A distressing situation is that of the patient who, usually after 10 or more years of taking insulin, begins to find that reactions occur without warning Symptoms of severe degree involving the central nervous system appear and are obvious to others but the patient, not having been warned by "adrenalin-like" symptoms,[13] is unaware of the trend of events. He may exhibit abnormal and irrational behavior, act as if an automaton, or lapse into stupor or unconsciousness with or without convulsions In prevention, admittedly difficult, the important points are careful regulation of the amount of insulin to avoid overdosage, the taking of adequate between-meal snacks and, in so far as possible, uniformity in the amount of physical activity taken daily.

Classification of Signs and Symptoms—The signs and symptoms of

grouped

getative

(*c*) are

psychical[14 15]

SYMPATHETIC NERVOUS SYSTEM—Belonging in this group are (1) Hunger and faintness (2) Muscular weakness Motion of arms and legs, speech and even standing may be difficult The extremities are as "heavy as lead" Tremor may be pronounced (3) Sweating Beads of sweat may appear on the forehead, and the palms, soles and axillæ often become moist The night clothes may be drenched, and if this occurs after an operation, leads to confusion with surgical shock Sweating is a valuable

A leukocytosis is not infrequent although one does not see values as

[13] Maddock and Krall A M A Arch Int Med, *91*, 695, 1953

[14] Wilder Deutsch Ztschr f Nervenh, *112*, 192, 1929, Klinik und Therapie der Zuckermangelkrankheit, Leipzig, Weidman & Co, 1930

[15] Falta P 118, loc cit, p 79

high as in diabetic coma. (6) Vomiting, representing, according to Falta,[16] a lowered tone in the splanchnic area and pains in the lower abdomen are

Central Nervous System.—(1) Those of bulbo-pontine character include chiefly disturbances of speech, inability to formulate words but ability to understand, mask-like facies, and slowness to react or lack of reaction of, or dilatation of, the pupils. (2) Symptoms of corticospinal origin include: Jacksonian twitchings, double vision, mono- and hemi-plegias, loss of reflexes, positive Babinski, involuntary micturition or defecation, severe tonic or clonic cramps (at times epileptiform), aphasia, amnesia, apraxia, and occasionally hallucinations. (3) Striothalamic symptoms may be akinetic or hyperkinetic. The patient knows he should take his sugar, but cannot take it out of his pocket and put it into his mouth. He may exhibit a fixed gaze and glassy eyes. Hyperkinetic symptoms include athetotic or choreiform motions, grimaces, loud speaking, a compulsion to cry, laugh or be ridiculous. (4) Central vegetative signs include: variations in regulation of temperature, somnolence, faintness, collapse, and temporary blindness

Psychical Manifestations.—These include loss of consciousness and may be followed by prolonged stupor. A patient may be stuporous rather *than comatose; although he understands what is said to him, he cannot* bring himself to expression. Other signs include catatonia and a state of excitement which may merge into actual dementia. Confusion with alcoholism is easy and therefore diabetics should leave alcohol alone. Psychoses, periods of hysteria, anxiety and depression, and attacks of violence, or attempts at suicide may occur The four-year old boy described by Haunz[17] was hysterical and complained of a sensation of worms crawling over the body The panicky child constantly tried to brush off the worms. Although symptoms persisted to an alarming degree for 8 hours despite chemical correction of hypoglycemia, there was no evidence of residual brain damage.

Storring,[18] in an analysis of 1200 insulin-treated diabetics, found that

treated schizophrenics, divides hypoglycemic symptoms in 5 groups whose unvaried order of appearance is explained on the basis of the metabolic rate of each region in the brain [21] According to Himwich, first to suffer from sugar deprivation are, phyletically speaking, the newest portions of the brain, the cerebral hemispheres and parts of the cerebellum, which *metabolize at the highest rate* Then, *in turn*, each succeeding lower portion of the brain becomes involved The medulla oblongata, the oldest

[16] Falta P 91, Loc cit p 79
[17] Haunz Jour Am Med Assn, *159*, 1611, 1955
[18] Storring Deutsch Med Wchnschr, *1*, 10, 1937
[19] Himwich Brain Metabolism and Cerebral Disorders, Baltimore, Williams and Wilkins, 1951
[20] Frostig Am Jour Psychiat, *96*, 1167, 1940
[21] Himwich and Fazekas Am *Jour Physiol*, *132*, *454*, *1941*

part of the brain and the portion with the lowest metabolic rate, functions long after higher centers are able to do so The 5 phases described by Himwich are: (*a*) cortical, (*b*) subcorticodiencephalic, (*c*) mesencephalic, (*d*) premyelencephalic and (*e*) myelencephalic. Naturally the fifth stage is the most dangerous and is recognized by deep coma and the predominance of parasympathetic signs. The patient's respiration is shallow, the heart rate is slow, the skin is pale and the pupils are contracted, no longer reacting to light Perspiration and a subnormal temperature are present. The muscles are relaxed, the tendon jerks depressed and the corneal reflex entirely lost. Prompt treatment is imperative

C IRREVERSIBLE DAMAGE TO THE CENTRAL NERVOUS SYSTEM

The signs and symptoms just described are due to the fact that in marked hypoglycemia the available supply of glucose falls below the minimal requirements of the tissues Under such conditions the *muscle* may have recourse to its stored glycogen, or may perhaps turn to protein and fat as a source of energy, but *nerve tissue* has little stored carbohydrate and cannot utilize protein or fat Therefore, nerve tissue during marked hypoglycemia is unable to maintain even the minimal rate of metabolism compatible with well-being Thus prolonged insulin hypoglycemia may lead to irreversible damage to the central nervous system An extraordinary example of this is to be found in the tragic case report which follows

10 cc of a 50 per

obtained

In one other patient it seemed likely that the psychosis observed had followed prolonged hypoglycemia. A brief account of the situation follows:

Mr A D, Case 37622, forty-seven years old with diabetes of over five years'

If hypoglycemic episodes are of brief duration, no such permanent damage need be anticipated It is true that Case 18919, a woman aged forty-two years when seen in 1940, showed such definite personality changes, loss of memory and inability to cerebrate normally six months after an attack of hypoglycemia with unconsciousness which lasted two weeks, that she

ever, she was a chronic

She died on May 13,

ath, occurring two days

he upper left humerus,

her physician wrote that over the years her mental status had remained unchanged. No autopsy was done and the physician could not with certainty state the cause of death.

Gardner and Reyersbach[22] attributed to repeated episodes of insulin hypoglycemia the progressive mental deterioration and organic brain damage with epileptiform seizure which they observed in a child with diabetes. Writing of prolonged attacks of hypoglycemia, Aitken[23] stated, "Although the intelligence quotient has been reported as dramatically improved[24] by the total relief of hyperinsulinism, some cases show marked residual deterioration." The persistence of serious mental changes is to be feared if *hypoglycemia is prolonged by reason of the giving of insulin* during a reaction mistakenly thought to be due to diabetic coma, as in the twenty-two-year old man described by Klein and Ligterink.[25]

In 40 healthy students aged seventeen to twenty-three years Davis[26] found that insulin in doses of 0.05 unit per kilogram of body weight produced the most dysrhythmia in electroencephalograms in those subjects in whom preinsulin records indicated slow dysrhythmic activity. The incidence of abnormal electroencephalographic tracings in insulin-treated diabetic parents in one series amounted to 8 per cent. (See page 503.) Of 35 of our diabetic patients who had had frequent severe insulin reactions, 18 had abnormal electroencephalograms.[27]

If a patient has a convulsion, one worries, fearing organic damage to the central nervous system. Residual signs, local paralysis, hemiplegia are alarming, although they may disappear within twenty-four hours. Allan and Crommelin[28] and Murphy and Purtell[29] each reported a child with evidence of residual cerebral damage. In certain cases a fall during a reaction or a supposed reaction complicates the picture because it may have nothing to do with a reaction, but prove to be a cerebral hemorrhage to which prolonged diabetes made the diabetic susceptible. The differential diagnosis here includes traumatic hemorrhage.

D. DEATHS DUE TO INSULIN REACTIONS

Deaths due to insulin reactions are relatively quite rare. Among 16,893 deaths reported among our patients since 1922 there were only 38 cases (0.2 per cent) in which the cause was listed as hypoglycemia and in certain of these the diagnosis did not rest on a sure basis.

Three patients, Cases 10292, 10444 and 13103, have died of hypoglycemia at the New England Deaconess Hospital. Each of these patients was comatose on admission to the hospital and, despite treatment which raised the blood sugar level to normal, died some hours later without regaining consciousness.

[22] Gardner and Reyersbach. Pediatrics, 7, 210, 1951.
[23] Aitken. Med Clin North America, 20, 393, 1936.
[24] Powell. Am Med, 40, 172, 1934.
[25] Klein and Ligterink. Arch Int Med, 65, 1085, 1940.
[26] Davis. Arch Neurol and Psychiat, 49, 186, 1943.
[27] Greenblatt, Murray and Root. New England Jour Med, 234, 119, 1946.
[28] Allan and Crommelin. Jour Am Med Assn, 118, 873, 1942.
[29] Murphy and Purtell. Am Jour Digest Dis, 10, 103, 1943.

In addition, a number of patients cared for by us at one time have died at home or in other hospitals while not under our immediate care. Some of these have been seen by members of our group in consultation during the final illness These patients included Cases 4735, 5045, 6884, 7167, 12882, 13904, 15295, 16455, 21142, 23161 and 30552 The history of Case 6884 is given below.

[illegible]

where she was transferred after several weeks of a vegetative existence at the Deaconess Senile plaques were found in the brain in addition to diffuse vascular disease and intercapillary glomerulosclerosis There were scattered necrotic cortical neurons[30]

In addition to the above, attending physicians ascribed to insulin hypoglycemia the death of Cases 2454, 4535, 5561, 5713, 5896, 9203, 12052 and 13859

Bowen and Beck[31] collected 19 fatal cases of insulin reactions in the literature, and Sigwald enumerated 24 cases.[32] Falta[33] referred to an instance of drowning during an attack of hypoglycemia. Lawrence, Meger and Nevin[34] report 6 fatal attacks and Roche[35] 2 fatal cases.

The experience of workers using insulin shock treatment for schizophrenia has been that occasionally patients remain comatose even after sufficient glucose has been given by gavage and by vein to raise the blood sugar to abnormally high levels This condition of protracted coma is a dangerous complication In patients recovering, the coma may persist for hours, days, or weeks, gradually merging into a state of catatonic stupor before awakening In certain patients fever, rapid pulse and respiration, convulsions, vomiting, and diarrhea may occur Death or permanent brain damage may result

Never blame insulin for a death unless to good clinical evidence is added the corroboration of a skilful and complete post-mortem examination! Case 2528, a twenty-six-year-old woman with diabetes of over fifteen years' duration, died suddenly eleven days after an appendectomy just as she was about to be discharged from the hospital Although at the time it was suggested that an insulin reaction might have been the cause of sudden death, autopsy disclosed a pulmonary embolism Another example was afforded in the experience with Case 1500 whose wife telegraphed as follows: "P B died early today from bad insulin reaction." We all doubted the *accuracy of the diagnosis and although a partial autopsy had been performed* to carry out our patient's desire to give us his pancreas, a second post-mortem examination was carried out the next day although it necessitated a trip of over 400 miles It proved well worth while because it revealed a typical acute coronary occlusion This patient had taken regular

[30] Hicks Arch Path *49*, 111, 1950
[31] Bowen and Beck Ann Int Med, *6*, 1412, 1933
[32] Sigwald Loc cit, p 316
[33] Falta Klin Wchnschr, *14* 697, 1935
[34] Lawrence, Meger and Nevin Quart Jour Med, *11*, 181, 1912
[35] Roche Brit Med Jour, *2*, 35, 1912

insulin for fourteen years; the onset of diabetes had been at the age of forty-one and death at sixty-three years.

It is rare indeed for a single dose of unmodified insulin even though quite

England to receive insulin, in August 1922, repeated by mistake her morning dose of insulin which consisted of 6 units of crystalline and 36 units of protamine zinc insulin. She was alone in the house. Unconsciousness resulted and continued from 1 A.M. to 4 P.M. when spontaneous recovery took place. There were no unpleasant sequelæ. She died in May 1947,

be confused with that of diabetic coma and more insulin given.

A remarkable case was that of Vogl and Youngwirth,[37] a sixty-three-year-old male diabetic patient who took 2000 units of protamine zinc insulin with suicidal intent. For 6 days thereafter it was difficult to attain and maintain a normal blood sugar level despite the continuous administration

resume insulin. Two weeks after admission he was again receiving his usual maintenance dose of 40 units of protamine zinc insulin. By this

disease *per se* but rather is dependent upon the doctor who treats it and the physical injury to which the reaction may expose the patient.

Any clinic in which large numbers of diabetic patients are treated is confronted often with insulin reactions, not only in patients in the hospital but in those previously, often quite recently, discharged. It is for this reason we ask our patients to carry an identification card in their pocket. See page 327.

It is much better to prevent than to be obliged to treat an insulin reaction. It is good prophylaxis to insist upon 10 grams of carbohydrate midway between meals and upon retiring, with double this amount during that portion of the day in which an automobile is driven. Diabetics taking insulin should avoid alcohol.

[36] Peck. Personal communication.
[37] Vogl and Youngwirth. New England Jour. Med., *241*, 606, 1949.

E. CHANGES PRODUCED BY LARGE DOSES OF INSULIN

The insulin dosage which can be tolerated without intoxication varies according to the species; for a strong man it is probably 15 units per kilogram and somewhat less for the dog and cat. For the rabbit it is 35 to 40 units per kg., for the mouse 1000, and for the rat 2000 to 4000 units, and for birds still higher.[38]

The widespread use of the insulin shock treatment for schizophrenia introduced by Sakel in 1928 has afforded much opportunity for studies of the changes taking place in the body as the result of the administration of large doses of insulin. Tietz[39] and co-workers found a consistent rise in blood adrenalin during the deep stages of insulin coma with a drop after termination.

Keyes[40] *studied the changes in the components of the blood serum in* otherwise normal male schizophrenic patients undergoing insulin shock treatment. At the height of the reaction the following changes were noted: (1) a moderate increase of protein, (2) a marked increase in potassium, (3) in all but one case a significant decrease in non-protein nitrogen, and (4) in all but one case a slight rise in the sodium. Studies in dogs gave similar results. The changes in the serum potassium were ascribed in large part to adrenal hyperactivity in response to hypoglycemia. Haid[41] reported a fall in blood calcium. Doust and Salna[42] studied the acute responses of the capillary vasculature in two nondiabetic males with schizophrenia who were given massive doses of insulin five times weekly for three months. They found as hypoglycemic coma developed, corpuscular flow rates in the skin capillaries fell significantly and progressively. Speed was regained when glucose was given and the coma interrupted. Skin temperature variations roughly paralleled these changes and suggested a similar influence on arterial blood flow. An increase in finger volume with the onset of coma suggested a waterlogging of the tissues.

Various workers have studied the anatomical changes brought about by prolonged hypoglycemia. These consist almost entirely of abnormalities in the central nervous system seen only on microscopic examination. Weil, [illegible]

there was evidence of marked shrinkage of the cytoplasm and nuclei. Zimmerman[44] studied the lesions of the nervous system in cats following large doses of insulin. The anatomical lesions included widespread cortical necrosis affecting the ganglion cells. When the hypoglycemia was of short duration the changes were apparently reversible and the animals recovered functionally and anatomically. Yannet[45] also studied the effect of insulin

[38] Allen ... Ibid., 219, 77, 1938.

... 1, 1940

hypoglycemia on cats In the muscles he found no significant changes in the distribution of water or potassium during or after severe hypoglycemia In the brain, however, there was a shift of water from the extracellular

[illegible]

of the surviving animals showed evidence of widespread cerebral damage with marked loss of cellular water leading to shrinkage of the cells and decrease in the concentration of intracellular potassium The total water content of the brain remained the same Moersch and Kernohan[46] found at autopsy in 2 cases of islet-cell tumor of the pancreas multiple petechial hemorrhages and degeneration of some of the nerve cells Layne and Baker[47] point out that any associated chronic disease that might affect the brain, such as alcoholism, arteriosclerosis, or prolonged chronic infection, will tend to make the patient much more susceptible to irreversible cerebral changes when marked hypoglycemia develops.

Sahs and Alexander[48] reviewed twenty-five articles describing changes in

[illegible]

in the cerebral white matter . Evidence is present to support the anoxic

[illegible]

brain, and, therefore, its metabolic rate were decreased during severe hypoglycemia.

F TREATMENT OF INSULIN REACTIONS

Treatment of an insulin reaction is simple and 5 or 10 grams of glucose orally usually relieve the patient in a few minutes Occasionally much more is required, and sometimes it is necessary to inject the glucose intravenously in which case, as a rule, the response is so prompt that before 10 cc of a 50 per cent solution are introduced recovery has occurred Indeed, the

[illegible]

drate is required, and in one of the fatal cases seen in consultation 200 grams of glucose were given intravenously and subcutaneously before the blood sugar began to rise Even then the damage may be done and the condition be irremediable

[illegible] 138

I rc [illegible] 1937 Himwich,

If the patient ... stomach tube ... the lungs. Gluc... and honey have all been used. Corn syrup can be given diluted with twice its volume of water by rectum with variable success. Warm liquids are preferable to cold.

Adrenalin will increase glucose in the blood provided glycogen is available in the liver. Consequently one can give to an adult, in a reaction which has occurred not too many hours after a meal, 1 cc. of 1 to 1000 solution of adrenalin or one-half this dose for a child. Pituitary extract (solution of posterior pituitary, surgical, U. S. P.) in dosage of 0.3 to 0. cc subcutaneously is likewise helpful. Even if the injection of adrenalin or pituitrin is effective, it should be followed by carbohydrate, because otherwise the recovery might be temporary. In our experience[40] glucagon given subcutaneously or intramuscularly in dosage of 0.5 to 1.0 cc (1mg. per cc) may be used in children who are unconscious or affected sufficiently to be unable to swallow or to cooperate. Doses of 1 to 2 mg. intramuscularly or intravenously were used effectively in adults by Elrich, Witten and Arai.[41] Glucagon, by causing glycogenolysis in the liver, will often raise the blood ...

Cases of extreme hypoglycemia with convulsions are treated with glucose but if the low blood ... may give 4 cc of 1... tion. If this does ... hour, one may employ constant intravenous administration of 10 per cent glucose solution to maintain the blood sugar at a level of approximately 200 mg. per cent. The use of hypertonic solutions of sodium chloride, sucrose, or sorbitol may be tried to combat cerebral edema if lumbar puncture indicates its presence. Oxygen under positive pressure is indicated if the patient has cyanosis. Suction may be necessary to aspirate fluid in bronchi resulting from pulmonary edema.

G. PREVENTION OF INSULIN REACTIONS

The following are helpful measures in the prevention of hypoglycemic reactions due to insulin: (1) Reasonable uniformity from day to day as regards diet, insulin and exercise, (2) careful adjustment of insulin program so that the type or types of insulin, dose and time or times of administration are suited to the individual patient, (3) regularly taken between-meal and bedtime snacks consisting of food requiring digestion and thereby providing slow absorption over an extended period of time, (4) frequent testing of the urine so as to foresee changing insulin requirements, (5) routine carrying of sugar, candy or other readily absorbable carbohydrate so that this may be ... the pocket or wallet or ... The form of the

[40] Marble and Garzon. Unpublished data.
[41] Elrich, Witten and Arai. New England Jour. Med., 258, 476, 1958.

indentification card issued by the American Diabetes Association is shown below. These may be obtained at 10 cents each by writing to the Association at 1 East 45th Street, New York 17, New York

I HAVE DIABETES

If unconscious or behaving abnormally, I may be having an insulin reaction.

If I can swallow, give me sugar, candy, fruit juice or a sweetened drink. If I am unable to swallow or if recovery does not take place promptly, call a physician or send me to a hospital at once.

Distributed by
AMERICAN DIABETES ASSOCIATION, INC.
1 East 45th Street, New York 17, N. Y.

(see other side of card)

● NAME ______ PHONE ______

ADDRESS ______ (STREET) (CITY) (STATE)

● PHYSICIAN ______ PHONE ______

ADDRESS ______ (STREET) (CITY) (STATE)

INSULIN TYPE	DOSE (units)
REGULAR	______
PZI	______
NPH	______
GLOBIN	______
LENTE	______

DATE ______

(see other side of card)

FIG 19 Identification card

Chapter 12

HYPERINSULINISM AND CHRONIC HYPOGLYCEMIA

Alexander Marble, M.D.

A. INTRODUCTION

Hyperinsulinism is a condition in which there is excessive secretion of

the injection of epinephrine, pituitary extract or glucagon. The symptoms are much the same as those caused by an overdose of injected insulin and vary quite as much from person to person and from attack to attack as is true in hypoglycemia artificially produced. Characteristically the patient with hyperinsulinism suffers periods of nervousness, trembling, sweating, weakness, unsteadiness of gait, emotional instability, inability to concentrate, bizarre behavior, mental confusion, and often increasing drowsiness leading up to total unconsciousness with or without convulsions. The con-

tumor. At any rate,
hat state in which
of islet tissue.[1] In
nd other forms of
diseases of the liver
affecting glycogen storage and conditions associated with hypofunctioning of the adrenal cortex, the anterior lobe of the pituitary and the thyroid.

B. TUMORS OF ISLANDS OF LANGERHANS

Incidence. Although in 1902 Nicholls[2] reported the finding of an adenoma of the islets
able to collect 20 such
not appreciated. In
"hyperinsulinism" but it was not until 1927 that the first case of hypo-

America, 28, 985, 1941.

glycemia (with recurring attacks of convulsions and unconsciousness and fatal issue in hypoglycemia), due to a tumor (carcinoma) of the islands of Langerhans, was reported with operative and necropsy findings by Wilder and associates from the Mayo Clinic.[5] During the last few weeks of the life of the patient, a physician, hypoglycemia was so severe as to necessitate the taking of 1000 grams of cane sugar daily. Metastases in the liver had developed, and potent insulin was obtained subsequently from these. This finding incidentally, was conclusive proof that insulin is the product of the beta cells of the islands of Langerhans. The first report of the cure of a patient by surgical removal of an islet cell tumor was made in 1929 by Howland, Campbell, Maltby and Robinson.[6] The growth was thought at the time to be malignant but ten years later the patient was in good helath.[7] Since these early reports, the literature on the subject has become voluminous. Because of repetitions in the publication of cases, it has been difficult for those writing on the subject to avoid certain duplications in the compiling of statistics.

In 1949 there appeared reviews of the literature by Leech and Noble,[8] who found 130 successfully treated cases of islet cell adenoma, and by Crain and Thorn,[9] who summarized the findings in 258 cases of functioning islet cell adenomas. In 1950 was published the paper of Howard, Moss and Rhoads,[10] who surveyed the literature which at the time of their study disclosed records of 398 patients with islet cell tumors. The authors presented the data regarding these cases in tabular form, dividing them into the groups shown in Table 60.

As with many conditions, more careful study has shown the incidence to be greater than has been ordinarily supposed. Thus, Lopez-Kruger and Dockerty[11] found a total of 44 islet cell tumors among 10,314 consecutive autopsies at the Mayo Clinic, only 8 of these gave evidence of functioning. This represents an incidence of 1 in 234 cases and is appreciably higher than the commonly quoted figure of 1 in 500 or 1 in 1000 autopsies. It is obvious from the data of the Mayo Clinic workers, as well as from that of others, that most islet cell tumors do not function and are found only by careful search at post-mortem examination (including histological study). In fact the estimate has been made that only about 20 per cent[8,12] of islet cell tumors function. Howard, Moss and Rhoads[13] concluded that the incidence of nonfunctioning adenomas is about half that of functioning tumors. Some of these are extremely small, being only a few millimeters in diameter.

Tabulation of data by various reviewers has shown that although islet cell tumors may occur at any age from six and one-half weeks to sixty-eight years, the peak incidence lies between forty and fifty years. No

[5] Wilder, Allan, Power and Robertson: Jour. Am. Med. Assn., 89, 348, 1927.
[6] Howland, Campbell, Maltby and Robinson: Ibid., 93, 674, 1929.
[7] Campbell, Graham and Robinson: Amer. Jour. Med. Sci., 198, 445, 1939.
[8] Leech and Noble: Ohio State Med. Jour., 45, 707, 1949.
[9] Crain and Thorn: Medicine, 28, 427, 1949.
[10] Howard, Moss and Rhoads: Surg., Gyn. and Obst., 90, 417, 1950.
[11] Lopez-Kruger and Dockerty: Ibid., 85, 495, 1947.
[12] Brown, Nevill and Hazard: Surgery, 27, 616, 1950.
[13] Howard, Moss and Rhoads: Loc. cit. p. 329.

TABLE 60.—SUMMARY OF REPORTED INCIDENCE OF ISLET CELL TUMORS*
(From Howard, Moss and Rhoads[1])

Type of Islet Cell Tumor	*Removed at Operation*				*Found at Autopsy*				*Total*			
	Functioning	*Non-functioning*	*Not Stated*	*Total*	*Functioning*	*Non-functioning*	*Not Stated*	*Total*	*Functioning*	*Non-functioning*	*Not Stated*	*Total*
Benign adenoma	154	3	2	159	46	82	26	154	200	85	28	313
Suspiciously malignant (localized) tumor	40	1		41	2	5	–	7	42	6	–	48
Carcinoma (with metastases)	17	6	1	24†	5	5	3	13	22	11	4	37
Total	211	10	3	224	53	92	29	174	264	102	32	398

[1]Howard, Moss and Rhoads. Loc. cit., p. 329.
*The figures refer to number of *patients* concerned.
†Includes all carcinomas found at operation rather than only those resected.

significant sex difference exists in the incidence of benign tumors although among 24 malignant tumors, 63 per cent were in males [14]

Pathology.—Most adenomas occur in the tail and body of the pancreas. However, about one-fourth of tumors are found in the head of the organ. Thus among 254 functioning adenomas and suspiciously malignant tumors analyzed by Howard, Moss and Rhoads,[15] the location of tumors was as follows: head 66, junction of head and body 10, body 62, junction of body and tail 25, tail 84 and ectopic 7. Among an additional 20 tumors overlooked at operation the distribution was: head 8, body 3, tail 6 and ectopic 3. The distribution of tumors in the 76 cases reported from the Mayo Clinic by Briedahl, Priestley and Rynearson[16] was as shown in Table 61.

TABLE 61.—SITE OF ORIGIN OF ISLET CELL TUMORS IN THE PANCREAS

(From Briedahl, Priestley and Rynearson)

Site of Origin	*Cases*	*Per Cent*
Head	19	25
Body	22	29
Tail	28	37
Junction of body and tail	4	5
Multiple	2	3
Not stated	1	1
Total	76	100

Aberrant locations have been chiefly in the duodenal wall, around the hilus of the spleen and posterior to the pancreas. As Howard *et al* point out, theoretically an adenoma might be in any of the areas where ectopic pancreatic tissue is found, such as in Meckel's diverticulum, in the wall of [illegible]

that no more than one nodule can be seen or palpated. Usually multiple tumors are found in the same general region of the gland but they may at times be widely separated. In Maxeiner's[17] case clinical recovery from attacks of hypoglycemic seizures followed removal of 75 per cent of the pancreas which on examination was found to contain 8 small islet cell tumors.

Most of the reported adenomas have varied in size from 1 to 2 cm. in diameter, although some have been quite small and others quite large. Lopez-Kruger and Dockerty[18] state that it is most unusual for a functioning tumor to be less than 5 mm. in diameter, however even among their own group of Mayo Clinic cases, two of the functioning tumors were only 2.5 and 4 mm. in diameter respectively. They state that when a functioning adenoma attains large size, the bulk of the tissue is made up of fibrous and

[14] Crain and Thorn. Loc. cit., p. 329
[15] Howard, Moss and Rhoads. Loc. cit., p. 324
[16] Briedahl, Priestley and Rynearson. Ann Surg. *142*, 698, 1955. Jour Am Med Assn. *160*, 198, 1956
[17] Maxeiner. Journal-Lancet, 65, 256, 1945
[18] Lopez-Kruger and Dockerty. Loc. cit., p. 329

hyalin elements In Brunschwig's case[19] the tumor was 13 × 10 cm and in its ... case reported by ... suring 11 × 9 × ... -pink or pur- pli... ng pancreatic tissue. The histological appearance of islet cell adenomas has been described by various workers, including Laidlaw,[21] Duff,[22] Lopez-Kruger and Dockerty[23] and others. Structurally the adenomas resemble gigantic islets ... al islet cells ... s, 1 to 4 cells ... blood vessels is a delicate fibrous connective tissue framework and this is condensed in the form of a thin or thick capsule about the periphery of the tumor. However, not infrequently the capsule is incomplete or absent.[24] In fact, microscopic examination of tumor tissue from our own 8 patients with adenomas showed the capsule of the tumor to be incomplete in each of 6 cases in which there was enough tissue available for satisfactory examination. In 1 of the 8 cases, questionable blood vessel invasion was noted.

TABLE 62.—PATHOLOGIC FINDINGS IN 91 CASES OF HYPERINSULINISM SEEN AT MAYO CLINIC, 1927–53

(Adapted from Breidahl, Priestley and Rynearson[16a])

Condition	*Tumor Found at First Operation By* — *Surgeon*	*Pathologist*	*Tumor Found at Second Operation*	*Tumor Found at Necropsy*	*Total Cases*
Adenoma	37	6	0	3	46
Grade I carcinoma	21	1	1	0	23
Metastasizing carcinoma	6	0	0	1	7
No tumor found		–	—	—	15
Total	64	7	1	4	91

The experience of the Mayo Clinic in this regard is summarized in Table 62. It will be noted that there were *23* cases of "Grade I carcinoma." The authors state that "such a lesion appeared malignant histologically but it was never found to metastasize, and clinically it behaved as a benign tumor."

The above discussion illustrates the difficulty experienced at times histologically in differentiating between malignant and benign islet cell tumors.

[19] Brunschwig Surgery, *9*, 551, 1941
[20] O'Leary and Womack Arch Path, *17*, 291, 1934
[21] Laidlaw Am Jour Path, *14*, 125, 1938
[22] Duff Am Jour Med Sci, *203*, 321, 1942
[23] Lopez-Kruger and Dockerty Loc cit p 329
[24] Uger and Putzki Med Ann Dist Columbia, *24*, 163, 1955
[16a] Breidahl, Priestley and Rynearson Loc cit p 331

The situation was discussed by Frantz,[25] who suggested that such tumors

sion of tumor tissue into tiny blood vessels does not necessarily indicate a malignant or pre-malignant state. In 1944 Frantz[25] stated that "in the group of suspicious tumors, the suspicion of the pathologist, not the surgeon, has yet to be confirmed in a single case by follow-up data."

Diagnosis.—Whenever marked hypoglycemia with values below 60 mg. and most certainly below 50 mg. per 100 cc.* regularly develops upon

and the condition regarded as not proved to be of pancreatic origin,[27] although such may well be the case.

No elaborate diagnostic procedures are necessary. The characteristic

matic hypoglycemia varies from two or three up to twenty-four hours or longer, depending upon various factors including the state of nutrition, the composition of the last meal, the amount of physical exertion and particularly upon the level of functional activity of the islet cell tumor concerned. Usually an overnight fast of eight to twelve hours suffices. As an aid in the diagnosis, the glucose tolerance test is of value only if carried out for a sufficient length of time, i.e., five or six hours. Characteristically, the blood sugar (fasting) starts at a low level, below 50 mg. and usually approximately 40 mg. per 100 cc. Following the giving of glucose, the rise in blood sugar may be within normal limits or the curve may be diabetic in type.[28] Conn and Conn[29] state that the type of curve depends upon the amount of carbohydrate in the diet of the preceding few days, diets high in carbohydrate increase sugar tolerance and those low in carbohydrate lower it. The glucose tolerance curve up to the third hour may, therefore, be

*Because most of the data given in this chapter were acquired prior to our adoption of the Somogyi-Nelson procedure, blood sugar values are those found by the Folin-Wu or comparable procedure. Values obtained by methods determining only "true" glucose would be 15-25 mg. lower.

[25] Frantz. Ann. Surg., *119*, 824, 1944.
[26] Porter. Jour. Am. Med. Assn., *142*, 1281, 1950.
[27] Keating and Wilder. Southern Med. and Surg., *103*, 125, 1941.
[28] Whipple, Bauman and Hamlin. Am. Jour. Med. Sci., *201*, 629, 1941.
[29] Conn and Conn. Arch. Int. Med., *68*, 876, 1941.

essentially normal or mildly diabetic in type except for the initial value. After three hours, however, the blood sugar usually falls rather sharply to a low level (in our cases usually to 40 to 50 mg. per cent) and in the fifth and sixth hours shows *no tendency to rise spontaneously* toward normal. This last fact is of importance: in the normal individual one often obtains a hypoglycemic phase in the glucose tolerance test but presumably due to the compensatory secretion of epinephrine, there is a spontaneous return to normal values. Such does not occur in hyperinsulinism probably because of the overpowering effect of the continuous secretion of insulin by the islet cell tumor.

The glucose tolerance curve in patients with islet cell tumors differs from that described by Portis[30] in patients with postprandial hypoglycemia associated with "vagotonia" and fatigue in the following particulars: (1) in the latter condition, the fasting blood sugar, although perhaps lower than the average normal, is not depressed to the extent seen in patients with islet cell tumors, (2) the curve tends to be flat; (3) the lowest blood sugar usually occurs two, three or four hours after the administration of glucose; and (4) there is a tendency for the blood sugar to return to normal without the administration of food or glucose.

Surgical Treatment.—Once the diagnosis of a probable islet cell tumor has been made, surgical exploration should be urged for the following reasons: (*a*) if one or more benign adenomas are found and removed, a complete cure may be expected, (*b*) "medical" treatment is usually unsatisfactory, (*c*) delay in surgery with continuance of hypoglycemic attacks may cause irreparable damage to the central nervous system, (*d*) delay may allow the development of increasing obesity due to the frequent taking of food to avoid hypoglycemic attacks. Such obesity renders surgical procedures more difficult. The possibility that transition from a benign to a malignant condition may occur has not been borne out by experience.

It is true that the patient reported by Murray and Tinsley[31] carried on for eight years without surgery. Hypoglycemia and loss of consciousness were controlled by dietary treatment and death took place from an unrelated cause. However, this experience is unusual and one must keep in mind that not only do insulinomas vary in the degree of activity but also, judging from symptomatology, a given tumor may vary in this respect from time to time.

The approach to the pancreas through a long curved transverse incision above the umbilicus, as advocated by Whipple,[32] has proved to be satisfactory. In the exploration one cannot overemphasize the importance of freeing the pancreas thoroughly so that it may be palpated throughout its extent from the tip of the tail to the head, and so that it may be visualized over as large a part of its course as possible. This means that infinite pains and patience are required and that at times the operation will be a long one. Of our ten patients, three had been operated on previously by good surgeons and yet the tumor was overlooked. Palpation must be sufficiently thorough

[30] Portis, Loc cit, p 383
[31] Murray and Tinsley Stanford Med Bull, *13*, 80, 1955
[32] Whipple and Frantz Ann Surg, *101*, 1299, 1935

and delicate that a tiny nodule embedded within the substance ... e pancreas and not visible from either surf...

In the patient ... in two operat ... moved, and ... deep within the remaining panc ... to the common bile duct ... t sure of the diagnosis prior to ... to the ... has bee ... high inc ...

Auth ... insulinism—Between 1939 and 1941 we encountered 6 proved cases of hyperinsulinism due to islet-cell tumors One of these, Case 4 (Table 63), was seen at the Massachusetts General Hospital In 5 of the 6 cases, removal of a *single adenoma* resulted in the relief of symptoms which has persisted to date ten to thir... operation In one patient (Case ? ... tion which disclosed an islet cell c... liver All operations were perfo ... associates Four of the patients were ... two were males The ages at *the time of operation ranged from sixteen to fifty-nine years* The period from the onset of symptoms to the time of operation varied from two to eight years In 4 cases the tumor was in the head, in one in the body and in one in the tail of the pancreas Two of the patients, Cases 1 and 5, had been operated upon previously without the finding of a tumor The case histories have been reported in detail elsewhere [39]

Since 1941 we have seen ... tumors, three benign a ... , 8, 9 and 10 in Table 63 T ... and 8 were given in detail in the preceding (ninth) edition of this monograph At that time Case 9, a man with previously well documented diabetes, was discussed but the diagnosis as regards a possible islet cell tumor was not clear Consequently, the case summary, including recent developments, is given below

Case 9 (Joslin Clinic No 39557), *J E K*, was admitted to the New England Deaconess Hospital on December 5, 1951 * He was then 46 years old According to the history given by the patient and his home physician, diabetes had been discovered in January 1933 at which time treatment with a restricted diet an... had been instituted During the early part of his treat... mately 50 units of insulin daily ... and later as a single ... had been obliged to ... October 1947 was tak ... protamine zinc insulin daily At about this ... spells of weakness relieved by candy or orange juice Since 19.. there had been an increased frequency and severity of these insulin reactions Since about July 1949 there had been periods of extreme weakness with marked mental confusion In the two and a half years from July 1949 to De-

*Many of the data were kindly supplied by Dr L W Roe and Dr Howard S J Walker Jr of Mobile Alabama

[36] Isaacs Jour Am Med Assn *130*, 401, 1946
[37] Fisher Gaus and James A M A Arch Path, *60*, 628, 1955
[38] Duff Loc cit, p 132
[39] Marble and McKittrick New England Jour Med, *235* 637, 1946

TABLE 63.—DATA REGARDING AUTHORS' 10 CASES OF PANCREATIC ISLET-CELL TUMOR

Serial No.	*Case No.*	*Sex*	*Age at Onset of Symptoms Yr.*	*Age at Operation*	*Lowest Fasting Blood Sugar mg./100 cc.*	*Date of Operation*	*Location of Tumor*	*Size of Tumor mm.*	*Type of Tumor*	*Remarks*	*Date of Last Report (or Death)*
1	1575	F	11	16	28	1/16/39	Head	12 × 11 × 9	Adenoma	Second operation	Died of leukemia September, 1957
2	1728	F	41	49	28	6/28/39	Body	15 (diam.)	Adenoma		March, 1958
3	1421	F	55	59	21	9/16/39	Tail	18 × 18 × 13	Carcinoma (mixed-cell type)	Died 11/3/39	
4	M.G.H.	F	26	29	25	10/7/40	Head	—	Adenoma		March, 1958
5	2811	M	30	32	33	10/31/41	Head	15 × 15 × 17	Adenoma	Second operation	Died Myocard. infarct. July, 1956
6	2812	M	43	45	48	11/18/41	Head	10 (diam.)	Adenoma		March, 1958
7	5458	F	72	73	31	4/23/48	Head	—	Carcinoma	Died on operating table	
8	5859	F	43	44	32	3/14/49	Body	17 (diam.)	Adenoma		March, 1958
9	30557	M	41	49	32	2/12/55	Body	20 × 20 × 17	Adenoma	Second operation	March, 1958
10	7058	F		35		2/21/54	Tail		Adenoma		February, 1958

[illegible] 1931 there had been a gradual accentuation of symptoms so that an episode [illegible]

Time	*Sugar in Urine Per Cent*	*Blood Sugar mg per 100 cc.*
Fasting	0	41
1 hr after glucose	0	164
2 " " "	0	168
3 " " "	0	132
4 " " "	0	80
5 " " "	0	65
6 " " "	0	51

[illegible]

Case 10 (Joslin Clinic No [illegible]) [illegible]

[illegible] ing Accordingly the patient was placed on a high carbohydrate diet for four days and the studies repeated This time during a glucose tolerance test, the blood sugar

culture However, despite constant drainage from the flank wound, fever continued so that on May 5, she was again operated upon A large mass, a subdiaphragmatic abscess, was found behind the stomach and drained After discharge from the hospital on May 22, drainage from the operative wound continued for some weeks *Finally, however, the wound closed and completely healed* When last heard from in February, 1938, the patient had been entirely well for the past few years with no recurrence of hypoglycemic symptoms

Functioning Islet Cell Tumors Occurring in Diabetic Individuals. —There would appear no reason why islet cell tumors, benign or malignant, might not occur in individuals with diabetes just as in non-diabetics. Our own experience in Case 9, described on page 335, indicates that this does indeed take place As early as 1934 Jacobsen[37] and in 1935 Bickel, Mozer and Junet[38] reported cases in which known diabetics developed symptoms and signs of hyperinsulinism which were later shown to be due to carcinoma of islet tissue, with in each case metastasis or extension to the liver.

In the 65-year-old diabetic woman whose case was reported by Hensler

5792 and 27816) in which unsuspected non-functioning adenomas were found in diabetic patients at post-mortem examination.

C HYPERINSULINISM WITHOUT ISLET CELL TUMOR ("FUNCTIONAL HYPERINSULINISM")

Generalized Hypertrophy or Hyperplasia of Islet Cell Tissue —As has been previously mentioned, certain patients in whom the diagnosis of a pancreatic tumor seemed likely from the clinical findings have been found at operation to have no tumor Some surgeons, first of whom were the Finneys,[40] *encountering such a situation, have carried out resections of the* pancreas following the principle of subtotal thyroidectomy for hyperthyroidism Such a procedure definitely assumes that the hypoglycemia is due to an excessive secretion of insulin.

*One should certainly be most cautious in making the diagnosis of hyper*insulinism without islet cell tumor In making such a diagnosis in the patient who has not been surgically explored, one takes for granted, first,

[37] Jacobsen Arch Path, *18*, 135, 1934
[38] Bickel, Mozer and Junet Bull et mém Soc méd d hôp de Paris, *51*, 12, 1935
[39] Hensler and Hartmann Schweiz med Wchnschr, *86*, 630, 1936
[40] Finney and Finney Ann Surg, *88*, 584, 1928

that there is no islet cell tumor present and, second, that the hypoglycemic attacks are not due to disturbances outside the pancreas. Even in those patients in whom no tumor can be found at operation, the possibility always exists that the growth is so small or so well hidden that it has been overlooked. That this is a real possibility has been amply shown by the experience of surgeons who more than once at second operations have found tumors overlooked at the first exploration.[41] Three of our patients (Cases 1, 5 and 9) are cases in point. The possibility of the presence of an adenoma in aberrant pancreatic tissue must likewise be considered.[42]

On the other

complete relief

that the proce

Edwards, Pessel, Rathwell and Wise[45] reported reversal of symptoms following resection of two-thirds of the pancreas in a woman in whom there had been marked aggravation of hypoglycemia in the premenstrual period. Experience has shown that to be successful, resection must be radical with removal of two-thirds to three-fourths of the gland.[46] Not infrequently in cases of resection, minute examination of the portion of the pancreas removed at operation has revealed one or more tiny adenomata which were not identified by the surgeon. If no tumor is found in the resected portion of the pancreas, the chances of cure are reduced greatly. In their survey of the literature, Howard *et al.*[47] found reports of subtotal resection in 77 patients. Cure was reported in 42.9 *per cent* and definite

46 patients (11 of these patients were later found to have an adenoma); in only 8 patients was "hyperplasia" and in another 5 patients "hypertrophy" of islet cells found. Of the remaining 18 patients, in 12 histological examination disclosed an islet cell tumor, in 2 chronic pancreatitis, in 1

resection was relatively high, 14.3 per cent, with pneumonia, atelectasis and peritonitis the chief causes of death.

"Neurogenic" Hypoglycemia. - The recurring hypoglycemia described by Portis[48] and others[49-51] in association with "vagotonia" and chronic fatigue has been discussed on pages 333 and 334. There is not general

[41] Whipple. Surgery, *16*, 289, 1944.
[42] Holman, Wood and Stockton. Arch. Surg., *47*, 165, 1943. See also Howard, Moss and Rhoads. Loc. cit., p. 329.
[43] Landry and Burns. Conn. Med. Jour., *13*, 729, 1949.
[44] Greenlee, White and Phillips. Jour. Amer. Med. Assn., *149*, 672, 1952 (5 months old baby).
[45] Edwards, Pessel, Rathwell and Wise. Am. Jour. Obst. and Gynec., *70*, 1120, 1955.
[46] Brush and McClure. Ann. Surg., *120*, 750, 1944.
[47] Howard, Moss and Rhoads. Loc. cit., p. 329.
[48] Portis. Loc. cit., p. 333.
[49] Donnelly and Palmer. South. Med. and Surg., *106*, 363, 1944.
[50] Conn. Jour. Amer. Med. Assn., *134*, 130, 1947.
[51] Perkins, Desforges and Guttas. New England Jour. Med., *243*, 281, 1950.

agreement as to the cause of this type of spontaneous hypoglycemia. Wilder[32] suggested that it might be the result of direct nervous influence on the glycogen mechanism of the liver. On the other hand, Conn regards this condition as one of functional hyperinsulinism in which there exist a hypersensitivity and an excessive "respon[illegible] islet cells to the nor[illegible] by Conn consists of [illegible] and high in protein [illegible] the fat content adjusted to the caloric needs of the individual. Portis gives somewhat more carbohydrate, arranges for between-meal and bedtime feed[illegible]

[illegible] (Functional Hyperinsulinism).—As with "neurogenic" hypoglycemia, one cannot be dogmatic as to the classification of this type of hypoglycemia. Conn regards it as the "normal response of the normal pancreas to an abnormally great stimulus," namely the unusually rapid absorption of sugar following the taking of food with consequent elevation of the blood sugar [illegible] which, following the [illegible] a normal blood sugar [illegible] 100 cc.) because of ex[illegible] absorption. He postulates that this results in a marked stimulus to insulin secretion which [illegible] hypogly[illegible]

[illegible] functional hyperinsulinism consists of a restricted carbohydrate, high protein diet with a six meal regimen if found helpful by the patient.

Factitious Hyperinsulinism.—*The surreptitious self-administration of insulin in large doses so as to produce repeated attacks of* [illegible]

[illegible] known diabetic, or anyone who has a special knowledge of diabetes, *insulin* and the *technique of hypodermic injection.* We have encountered one proved case of this type

Case 4076 with onset of typical juvenile diabetes at the age of [illegible]

[illegible] than C 200, P 100, F 100 grams a day. She re-entered the hospital in March 1936 for special studies which showed a *curious*

[32] Wilder P. 357, loc cit, p. 71
[33] Conn and Seltzer Am Jour Med, 19, 460, 1955
[34] Rynearson Paper presented at the annual meeting of the American Diabetes Assn, Atlantic City, June 1951

insulin was ad-
which at times
se tolerance test

937. She stated

though no insulin had been taken

On January 6, 1944 at an office visit the urine contained 2 6 per cent sugar and [illegible]

California on August 15, 1955 in cardiac failure.

D NON-SURGICAL TREATMENT OF HYPERINSULINISM

[illegible]

patients, with those in whom exploration fails to reveal a tumor and with those who refuse surgery, non-surgical treatment must be resorted to This consists not only of therapy for acute attacks of hypoglycemia but also measures taken to prevent their frequent occurrence

In acute attacks relief is best secured by the administration of carbohydrate in a form easily available to the body If the patient is able to cooperate, orange or [illegible]
may be given by mou
(10 to 20 cc of a 50 p
relief The administration of 0 5 to 1 0 cc. of epinephrine, pituitary extract or glucagon subcutaneously may be of assistance just as in patients experiencing hypoglycemia due to injected insulin

In the prevention of att[illegible]
protein,[63, 64] has been foun
tageous but care must be

[63] Conn Jour Clin Invest, 15, 673, 1936
[64] Conn and Conn Arch Int Med, 68, 876, 1941.

of fat. The total food supplied for the day is best divided into 3 main meals and 3 snacks; the snacks, given in the forenoon, afternoon and at bedtime, should be made up not of pure carbohydrate as fruit juice or ginger ale but [illegible]

and lesser physical manifestations although it is doubtful that hypoglycemia is appreciably altered. Epinephrine, ephedrine, thyroid extract, extracts of posterior pituitary, bromides, atropine or belladonna and caffeine have also been suggested but their use either does not give relief or produces other effects in the body which make their continued administration undesirable.[57]

Conn and Seltzer[58] believe that for two reasons the patient should be prepared for surgery with corticotrophin or hydrocortisone: (1) to elevate the blood sugar by inducing insulin resistance and (2) to attempt to prevent "idiopathic hyperthermia" which was present in 5 of the 18 postoperative deaths found by Howard, Moss and Rhoads[59] in their review of the literature.

Theoretically, at least, alloxan might be of value in the treatment of hyperinsulinism. A number of years ago Brunschwig and his associates[60] injected alloxan into a thirty-two year old man with an islet cell carcinoma of the pancreas with metastases to the liver. Temporary improvement lasting several days and in one instance twenty-one days, during which no hypoglycemic reaction occurred, followed each series of injections. However, the untoward effects of the injections were so marked that the patient refused further treatment of this type. At autopsy, histological examination showed no effect on either normal islets or tumor tissue.[61] In Priestley's[62] case, jaundice followed a series of injections of alloxan and at autopsy extensive parenchymal damage to the liver was seen. In the patient of Fisher, Gins and Janes,[63] alloxan produced only temporary elevation of the blood sugar and symptomatic relief. Toxic side effects were marked and a final injection of 150 mg. per kg. of body weight was followed by shock, dyspnea, cyanosis, hyperpyrexia, jaundice, coma and death. At autopsy there was no evidence of effect on either normal islet tissue or tumor. The consensus of those who have used alloxan in human subjects is that it is a highly toxic, dangerous drug which can be expected to yield little or no beneficial results in patients with islet cell tumors.

Since physical activity accentuates the tendency to hypoglycemia, exercise must be taken in moderation. Before periods of unusual exertion, additional food, preferably of a type requiring some digestion, should be taken prophylactically.

In the treatment of hypoglycemia not due to injected insulin or to hyper-

[57] Wilder, R. M.: Loc. cit., p. 71.
[illegible]
Am. Med. Assn., 124, 212, 1944.
et al., Loc. cit., p. 332.

insulinism (see Section E which follows), therapy must be directed toward the underlying cause.

E CHRONIC SPONTANEOUS HYPOGLYCEMIA ARISING OUTSIDE THE PANCREAS

fibromas and sarcomas, (8) possibly as an early manifestation of diabetes, and in miscellaneous conditions

Undernutrition.—The low diet of the Allen undernutrition era pre-

although already low, took place shortly prior to the hypoglycemia In 2 instances the excretion of urinary nitrogen was excessive

death occurred in Case 14122, whose diabetes of 16 5 years' standing formerly required 36 units of insulin daily for control At autopsy macrofollicular lymphoma was found Hypoglycemia undoubtedly occurs in afebrile cachexia, certainly some of the symptoms of cachectic patients are explainable on this basis

Hypoglycemia is well known in the newborn infant and during lactation, in the course of diarrhea and even of a slowly absorbed meal from whatever cause Sigwald[65] cites its occurrence as a result of cold or dehydration. Consider its possible wholesale occurrence in famine and in voluntary starvation, as practiced by religious fanatics in olden times, and how comparatively easy it would be for ascetic monks or magicians to go into a trance, see visions and dream dreams at the conclusion of a physical orgy of ecstatic fury What a field for physiological interpretation of the past! And there is a quasi humorous or practical side universally recognized in never trying to make a bargain or to seek a contribution for research or the hospital when the prospect's stomach is empty and hypoglycemia present

That hypo-

below 40 mg

undernourish

[64] Joslin Loc cit, p 314
[65] Sigwald Loc cit, p 316
[66] Gounelle and Marche Occupational Med., 1, 48, 1946

observations were made on individuals who were on inadequate diets in France in 1941 and 1942. Of particular interest was the occurrence of spontaneous hypoglycemia in persons whose diets were deficient in protein and fat and not in carbohydrate.

Exercise.—Levine and his associates[67] found the blood sugar to be moderately diminished in 2, and markedly diminished in 4, of 11 Marathon runners studied. A close correlation existed between the physical condition of the runners at the finish of the race and the level of the blood sugar. Those competitors who had extremely low blood-sugar values presented a picture of shock, not unlike that produced by an overdose of insulin. Blood-sugar figures as low as 49 and 50 mg. per cent were obatined, but when these same individuals ate candy during the run the percentages were 92 and 114 mg. per cent and they finished in good condition.

Soon after the beginning of exercise there is an initial rise in blood sugar, as Lev[illegible]
This ri[illegible]
but if [illegible]
the same manner as that of a normal individual or mild diabetic who can secrete enough of his own.

Conditions Affecting the Suprarenal Glands.—A low blood sugar is often found in Addison's disease and has been referred to by Wadi[69] and Porges.[70] A case of Rabinovitch and Barden[71] who died in hypoglycemia was found at autopsy to have the adrenal medulla entirely replaced by lymphoid tissue. Anderson's case[72] of fatal hypoglycemia had an adrenal tumor. See page 645

The occurrence of hypoglycemia in congenital adrenal hyperplasia has been reported by White and Sutton[73], Wilkens *et al.*[74] and Conn and Seltzer.[75] The last-named workers recommend hydrocortisone as the treatment of choice in this condition. Cortocotrophin is contraindicated.

Hypothyroidism.—Hypoglycemia of mild degree may occur in cases of thyroid insufficiency. Such has been reported by Campbell,[76] Gardiner-Hill,[77] Zubiram[78] and Holman.[79] Goldzieher,[80] in studying 112 cases of hypoglycemia, stresses the importance of pituitary and thyroid lesions. McQuarrie[81] reported a case of severe hypoglycemia responding to thyroid substance. Such hypoglycemia is rare or of little clinical importance, however.

[67] Levine, Gordon and Derick. Jour. Am. Med. Assn., *82*, 1778, 1924. Gordon, [illegible] Ibid., *85*, 508, 1925.

[illegible] *184*, 494, 1932.

[illegible] Metab., *11*, 1395, 1951.
[illegible] Ibid., *12*, 1015, 1952.

[illegible] [illegible]ed., *18*, 327, 1925.
[illegible] Harris. Ann. Int. Med., 7, 1084, 1934.

[79] Holman. Bull. Johns Hopkins Hosp., *34*, 69, 1923.
[80] Goldzieher. Endocrinology, *20*, 86, 1936.
[81] McQuarrie. Am. Jour. Dis. Child., *87*, 399, 1954.

5. Hypopituitarism.—The increased carbohydrate tolerance found in states of diminished pituitary secretion is discussed in Chapter 26 (page 624) Pituitary extract is an insulin antagonist and decrease in its effectiveness may well render an individual insulin-sensitive, just as Houssay [illegible]

[illegible]

terminal amelioration of diabetes occurred in a man with cerebral metastases from carcinoma of the larynx.

Wilder[85] has described a condition of *"hypophysare-spontanhypoglykamie,"* characterized by symptoms of hypoglycemia in association with pituitary disturbances. The woman, aged forty-eight years, with Simmonds' disease reported by Mogensen[86] had blood sugar values as low as 38 mg per cent. Lloyd's[87] patient who died in convulsions had a pituitary tumor and hypertrophy of the islands of Langerhans and of the parathyroid glands. Farquharson, Belt and Duff[88] found blood sugar values as low as 28 mg. per cent in 3 patients with Simmonds' disease

Disease or Removal of the Liver.—The sugar in the circulating blood has for its source the glycogen in the liver. When this glycogen reserve is depleted, hypoglycemia, unrelieved by the administration of epinephrine, pituitrin or thyroid extract, may result. The factor of safety is large, however, and Mann[89] has shown that permanent reduction of hepatic tissue to less than 15 per cent results in only slight changes in the blood-sugar level It is significant that in depancreatized dogs a fall in blood sugar occurs steadily following hepatectomy, as in the normal animal Briggs[90] cites 7 references concerning hypoglycemia in connection with destructive disease of the liver. Hypoglycemia is known to occur following toxic damage to the liver from chloroform, carbon tetrachloride and guanidine,[91] from phosphorus,[92] from hydrazine,[93] and following infections of the liver itself[94] Our own diabetic patient, Case 10182, with carcinoma of the rectum and undoubtedly metastases to the liver, developed recurrent hypoglycemia in the days preceding death despite the fact that insulin had been discontinued.

[85] Williams Diabetes [illegible]

[illegible] Clin Assn, 54, 106, 1938

[illegible] Minot Jour Pharm and Exp [illegible]

[92] Frank and Isaac Arch f exp Path u Pharmakol, 64, 274, 1911

[93] Underhill Jour Biol Chem, 10, 159, 1911 Bodansky Am Jour Physiol, 66, 375, 1923

[94] Lyon Acta med Orient, 4, 401, 1945

Coller [illegible] regard as [illegible] operation, [illegible] creas, a return toward normal dextrose tolerance was obtained.

Hypoglycemia Associated with Fibromas and Sarcomas.—In recent years there have been reports of cases of severe, recurrent hypoglycemia brought on by fasting and in whom at operation no islet cell tumor has been found but instead, a large fibroma or sarcoma. The tumors have been located usually in the abdomen but at times in the chest. Removal has in most cases resulted in prompt relief of hypoglycemia but recurrence of the tumor and hypoglycemia has often occurred. It has been suggested that these tumors cause hypoglycemia by consuming selectively large amounts of glucose. For further details see the articles by Skillern, McCormack, Hewlett and Crile,[96] Conn and Seltzer,[97] and Silvis and Simon.[98]

Early Manifestations of Diabetes.—Seltzer, Fajans and Conn[99] have called attention to a group of patients whose presenting symptoms are suggestive of hyperinsulinism but whose glucose tolerance tests disclose the presence of mild and usually unrecognized diabetes. They report findings in 110 patients in whom glucose tolerance tests were diagnostic of diabetes and yet exhibited a steep secondary hypoglycemic phase with low blood sugar values between the third and fifth hours of the test. In treatment they recommend control of diabetes with carbohydrate restriction, and in some patients the use of insulin. If present, obesity should be corrected.

Idiopathic Hypoglycemosis.—McQuarrie and co-workers[100,101] have called attention to a syndrome of spontaneous hypoglycemia in children which they term idiopathic hypoglycemosis. No etiology is apparent for the condition. Convulsions with or without coma are common manifestations and fasting blood sugar values as low as 10–15 mg. per 100 cc. were noted. Brain damage and mental retardation occur frequently. McQuarrie found treatment with corticotrophin to be beneficial. Gall and Burke[102] of the Mayo Clinic have reported two cases and Burke[103] has written further on the subject.

Chronic hypoglycemia occurs characteristically in von Gierke's disease (glycogen-storage disease, glycogenosis). In this condition the liver is enlarged and filled with glycogen. Yet despite this superabundance of carbohydrate stores in the body the individual suffers from want of usable sugar due presumably to diminution or lack in the amount of glycogenolytic enzyme or glycogenase in the liver. The fasting blood sugar is consistently low and fasting acetonuria, lipemia and hypercholesterolemia are not uncommon.[104] Interestingly enough in von Gierke's disease the patient

[95] Coller [illegible] 112, 128, 1939.
[96] [illegible] Diabetes, 3, 133, 1954.
[97] [illegible]
[98] [illegible] Med., 254, 14, 1956.
[99] [illegible] 437, 1956.
[100] [illegible] Bull. Univ. Minn. Hosp. and Minn.
M[illegible]
[101] [illegible] 1, 1953.
[102] [illegible] Clinic, 30, 477, 1955.
[103] [illegible]
[104] [illegible] 34, 1946.

may experience no symptoms as a result of the hypoglycemia, even though the blood sugar may be extremely low Wagner's monograph[105] on "*Die Speicherkrankheiten*" was an early classic in this field

Other Conditions.—McCrudden and Sargent,[106] Sendrail and Planques,[107] and Scheimann[108] have reported low blood-sugar values in progressive muscular dystrophy MacLean and Sullivan[109] noted hypoglycemia in patients with status thymolymphaticus, although seldom, if ever, were blood-sugar values low enough to provoke symptoms

Herrmann and Gius[110] found at operation in their patient not an adenoma but a calcareous mass in which no pancreatic tissue could be found Removal of the mass apparently overcame the hypoglycemia. The man reported by Brinck and Sponholz[111] likewise was found to have pancreatic stones and in addition a marked degree of lipomatosis of the entire pancreas with almost complete disappearance of the acinar tissue. There was in addition atrophy of the liver with fatty infiltration

A tendency to hypoglycemia in individuals with renal glycosuria has been described[112] but has not been observed in our own patients

[105] Wagner Ergebn d inn Med u Kinderheilk, *53*, 586, 1937.
[106] *17*, 465, 1916
35, 1137, 1927 Cited by Moore *et al*.
l and Med, *23* 425, 1926
108, 1402, 1937.
dauungs- und Stoffwechselkrankh, *1*,

[112] Conn Loc cit, p 341

Chapter 13

DIABETIC ACIDOSIS AND COMA

Revised by HOWARD F. ROOT, M.D.

A. DEFINITION

DIABETIC coma is the unique complication of diabetes resulting from insulin deficiency and ketosis due to failure of diabetic control. Although the word "coma" implies the state of unconsciousness so profound that no stimulus [illegible]

late stages

Since acidosis varies widely in severity without sharp transition from one stage to another, arbitrary standards of classification must be set up. For some years it has been our custom to classify any case of diabetic acidosis as one of diabetic coma when the carbon dioxide combining power (or more recently, the carbon dioxide content) of the blood plasma is 20 volumes per cent (9 milliequivalents per liter) or less. This arbitrary division of cases is at times unsatisfactory, but it has the advantage of affording [illegible]

a CO_2 of above 20 volumes per cent recovered, most, though not all, of those with values below this died. Hence, our series include, in a rough sense, those patients who without the aid of insulin would have died.

Comparison of the mortality from coma in different clinics is of uncertain value, but we do believe that improvement in the treatment of coma year by year in one's own hospital should be the common aim

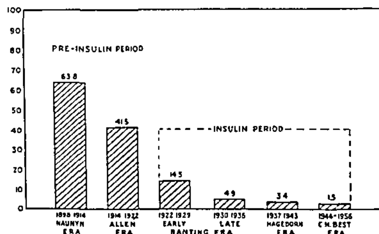
Deaths from coma have been greatly reduced but may still occur because of ignorance, delay in diagnosis or actual neglect. In recent years, changes in the electrolyte metabolism and especially hypokalemia have been recognized as grave complications sometimes occurring during ketosis and in the course of treatment. Fortunately, appropriate treatment may be given. Diabetic coma due to ketosis is (1) always an emergency, (2) always remediable, if treated early and adequately and (3) preventable

B. INCIDENCE

[illegible]

… from 1898 to 1914 died in

thors' diabetic patients, no matter where in the world they died, were in coma. (See Fig 20) Despite this markedly lowered incidence and mortal-



tality fell to zero

ity, diabetic coma still occurs all too frequently From May 1923, to January 1, 1957, we have seen in all 969 cases (in 719 patients) of diabetic acidosis in which the CO_2 combining power, or content, of the blood plasma was 20 volumes per cent (9 milliequivalents per liter) or below

Sixty-seven consecutive cases of severe and moderately severe diabetic acidosis treated over a period of five and a half years are reported by Harwood[2] Eight additional cases are mentioned subsequent to the writing of the paper of whom one died of potassium deficiency and peritonitis Pease and Cooke[3] analyzed 111 cases of pre-coma and 74 cases of full coma occurring in the years 1932 to 1950 In 23 fatal cases, 16 of whom had traveled from 6 miles to more than 21 miles to reach the Radcliff Infirmary in Oxford, only 4 had been given insulin before starting

[1] Joslin Bull Johns Hopkins Hosp, 29, 82, 1918, Med Clin North Am, 1, 1895, 1918

[2] Harwood New England Jour Med, 245, 1, 1951

[3] Pease and Cooke Brit. Med Jour, 2, 336, 1951.

Brakier and Brull[4] reviewed 180 cases of acidosis between 1924 and 1948 in whom the deaths numbered 56 or 31.1 per cent. When the CO_2 of the blood was above 20 volumes per cent, the mortality was only 20.3 per cent, and in those 34 cases where the CO_2 of the blood was below 20 volumes per cent the mortality was 55.8 per cent. From 1951 to 1954, in 64 cases, the mortality was 20 per cent. Zieve and Hill[5] report 124 patients from Minneapolis, of whom 71 per cent recovered and 29 per cent died in acidosis.

These reports force upon us the realization that diabetic coma is still an important problem. Since most cases are needless, efforts must be redoubled in order to educate the public and medical profession alike so that diabetic coma may be avoided.

C. ETIOLOGY

Diabetic ketosis results from an intoxication caused by the accumulation of excess products of intermediary protein and fat metabolism dependent upon insulin deficiency. Drowsiness and coma represent the reaction of the

shock; (5) vomiting and diarrhea from any cause; (6) thyrotoxicosis; (7) pregnancy and toxemias of pregnancy. In our experience, dietary errors are the most frequent among the etiologic factors in the development of ketosis. Gross dietary excess with increased hyperglycemia and glycosuria, like the omission of insulin, leads to ketosis.

The development of insulin resistance may render a very large amount of insulin ineffective. Case 17162 developed diabetic coma with a blood sugar of 430 mg. per 100 cc. and a CO_2 of 2.3 mm. per liter despite the fact, that in the few days just prior to the onset of coma, his insulin dose in the hospital under close observation had ranged from 300 to 480 units daily. During the 24 hours of treatment, 2,313 units of insulin were required and recovery followed. Infections acting as a contributing factor have included upper respiratory infections, pneumonia, carbuncle, abscesses, infections and gangrene of the foot, pulmonary tuberculosis, hepatitis, sinusitis, acute rheumatic fever, urinary tract infections, appendicitis, cellulitis of the neck, and meningococcus meningitis. Acute thyrotoxicosis ("thyroid storm") and diabetic c

has occurred

With insuff

a rapid rise in the blood sugar level and glycosuria occur. Loss of calories due to the faulty carbohydrate utilization stimulates the mobilization and utilization of protein and fat. The depot fat is mobilized, fatty acids are transported to the liver where conversion to ketone bodies takes place. Since it is not possible for fatty acids and ketone bodies to replace completely the caloric deficiency imposed by impaired carbohydrate utilization, the tissue needs are never satisfied and the stimulation for increased fat and

[4] Brakier and Brull. Rev. Méd. de Liège, 5, 7, 1950, Diabète 7, 146, 1955.
[5] Zieve and Hill. Arch. Int. Med., 92, 51, 63, 1953.
[6] Bertram. Die Zuckerkrankheit, 4th Ed., Leipzig, Georg Thieme, p. 81, 1953.

particularly sodium and potassium, are lost in the urine with the acid end-products The loss of this fixed base results in acidosis and dehydration

D CLINICAL MATERIAL IN DIABETIC COMA

The entire series treated by the authors at the New England Deaconess Hospital from May 1923 to January 1, 1957 includes, as stated above, 969 instances of coma in 719 patients From time to time reports have been published describing successive groups of these cases[3] In Table 64 are summarized the data given in articles published to date

The average age of patients varied in the different series only from 27 9 to 31 1 years Extremes of age are seen[1] Case 19034 was only eleven months while Case 7210 was 77 5 years of age at the time of coma For Case 7210 this was a third attack Both the baby and the elderly woman recovered and, as far as we have been able to discover, the latter is the oldest patient on record to have recovered from an attack of diabetic coma Case 6960 was 77 3 years of age when she recovered from coma in May 1943 In Dillon and Dyer's[4] series there was one woman aged eighty-three years who entered the hospital with a blood sugar of 806 milligrams and a CO_2 combining power of 18 volumes, per cent She died, however, eleven hours after admission and post-mortem examination showed abscesses of the kidneys and lungs

Among the 719 patients there were 247 males and 472 females The preponderance of females is all the more striking when one considers that in the childhood group diabetes is fully as common in males as in females

The duration of diabetes prior to the onset of coma varied from 1 2 years

[1] Bevan refers to 79 cases in infancy Brit Med Jour 2, 198, 1958

[2] Campbell and Best Metabolism 5, 95 1956

[3] Joslin et al Med Clin North Am 8 1873, 1925 10, 1281 1927 11 11, 1929 / 829 1932 11 793 1933 New England Jour Med 212 288 1935 Arch Int Med, 59 175 1937 Jour Am Med Assn 119 1160 1942 Penn Med Jour 56 355, 1953 Root Story and Cortesi New England Jour Med 245 765 1951 Root Jour Am Med Assn 127 557 1945 Stephens and Root Post Grad Med, 13 164, 1953, Root Jour Chronic Dis 2 121 1955

[4] Dillon and Dyer Ann Int Med 11, 602 1937

TABLE 64.—DIABETIC ACIDOSIS AND COMA

969 Cases 1923—Jan. 1, 1957—Summary Table

Series and Number of Cases	Age at Coma, Years	Duration of D. M., Years	Date	Blood: Sugar Mg. per 100 cc.		Blood: Plasma CO_2 mm. per Liter		Blood: Non-protein Nitrogen mg. per 100 cc.	Urine at Entrance	Insulin Units		Fatal Cases	
				1st Day	*2d Day*	*1st Day*	*2d Day*	*1st Day*	*Sugar Per Cent*	*1st Day*	*2d Day*	*No.*	*Per Cent*
I 179	30.9	3.2	1923–1931	499	200	6	29	51	3.4	205	50	27	15
II 284	29.1	4.0	1931–1940	503	171	5	14	41	3.7	205	61	28	10
III 188	27.9	6.3	1940–1946	500	150	6	17	51	3.3	202	71	6	3
IV 153	31.1	9.3	1946–1951	581	172	7	18	55	3.1	347*	30	5	3
V 165	29.0	8.5	1951–1957	531	145	6	17	40	3.2	324*	96	8	4.8
Total and Averages 969	29.2	6.6	1923–1957	519	167	6	15	49	3.3	263	72	74	7.6

*245 patients received in addition, 20–420 (avg. 73) units prior to admission on phone order.

[illegible]

[illegible] coma series by the inclusion of a great [illegible]

diabetes. The continued occurrence of coma in patients who have had [illegible]

It is not enough for a patient to be familiar with the technical details [illegible]

In 15 per cent of our cases of diabetic coma the disease had not been recognized until the onset of acidosis. Loeb[9] states that 5 of 7 fatal cases had no diagnosis of diabetes prior to coma. In the series of 124 cases of Zieve and Hill[10], 21 patients (17 per cent) and in Harwood's[11] series 15 patients out of 67 (23 per cent) had no diagnosis of diabetes prior to coma. Even more striking was the experience of Dillon and Dyer[12] in this respect, of their 224 patients with diabetic coma, 82 did not know that they had diabetes at the onset of acidosis which caused them to be admitted to the Philadelphia General Hospital. These cases present a difficult problem, and it is only by education and stimulation of the interest of physicians and laity alike regarding the importance of early recognition of the disease that progress can be made.

E. THE SYMPTOMS AND SIGNS OF DIABETIC COMA

Warning Signs and Directions to Patients.—The symptoms of diabetic coma are notoriously vague and even to a doctor the diagnosis often proves elusive. The spectre of threatening diabetic coma should always haunt the physician, particularly when the patient is first seen. It is astonishing how insidiously coma steals over a patient, and we have given up expecting nurses, unless they have had great experience with diabetic patients, to recognize its approach. It is better to treat any symptoms out of the ordinary as premonitory of coma and better for patients when they feel sick to begin coma precautions than to run the risk of beginning treatment too late. Despite the only too large number of cases of diabetic coma which we have seen, more than once we have been chagrined at having failed to realize its presence. Anything unusual should arouse

[9] Loeb: In Cecil and Loeb, Textbook of Medicine, 9th Ed., Philadelphia, W. B. Saunders, p. 669, 1955.
[10] Zieve and Hill: Loc. cit., p. 850.
[11] Harwood: Loc. cit., p. 349.
[12] Dillon and Dyer: Loc. cit., p. 351.

suspicion, and one should instantly investigate any of the following symptoms: headache, anorexia, restlessness, weakness, listlessness, nausea, vomiting, drowsiness, and painful, *rapid* or *deep* breathing. In the presence of fever always be on the alert for coma.

Rules for the prevention of coma are taught to all patients and they are instructed to follow them whenever they feel indisposed from any cause *whatsoever. These measures can do no harm in any condition and by* their adoption in the early stages of acidosis will avert it in all but the most desperate cases. They are as follows: (1) Go to bed whenever indisposed; (2) keep warm; (3) call the doctor after first having examined the urine for sugar; (4) secure a nurse or at least someone to wait upon you and save your strength; (5) drink a glass of liquid each hour—such as coffee, tea, broths, diluted orange juice, water, oatmeal gruel; (6) move the bowels by enema, and, if liquids have not been retained by mouth, follow the enema by an injection of 1 pint of lukewarm water containing a tea*spoonful of salt, (7) on the advice of your doctor take appropriate doses of* rapidly-acting insulin as long as the urine contains sugar.

Symptoms.—As stated above, there are no symptoms which are invariably found but usually the onset of definite acidosis is attended by headache, malaise, nausea, vomiting, abdominal pain and pains variously over the body including the extremities. Often these symptoms have been preceded by thirst, polyuria and other classical symptoms of uncontrolled diabetes. Useful in diagnosis is the history of irregularity in treatment with diet or insulin, of an infection or of a state in which there is *increased metabolism If proper treatment is not instituted the vomiting* and abdominal pain continue and the breathing becomes labored

The saturation of the body with "acetone bodies" is reflected in the fruity odor of the breath which sometimes is so marked that the peculiar smell in the sick room is apparent to those entering Drowsiness comes, proceeds to stupor and passes finally into coma. Complete unconsciousness [illegible] brought

[illegible]

tion of the plasma CO_2 combining power shortly after entrance gave a value of 4 volumes per cent(!) Energetic treatment with supportive measures and 430 units of insulin were of no avail and he died seven hours after admission In the pre-insulin days Case 1870 *walked* into the hospital at 9 A.M. February 11, 1921 Although marked Kussmaul respiration was present, the mental state was affected only to the point of drowsiness However, this patient was dead by 10 P.M., thirteen hours after admission

Signs.—When first seen, the patient in full-blown diabetic coma pre*sents a distressing picture He lies in bed, unconscious or semiconscious,* often moaning as with pain, with a dry, cold skin, flushed drawn face, and obviously dehydrated tissues One evidence of the dehydration may be a pleural friction rub, which may disappear rapidly with the administration of fluids, as was described by Armanino and Ory[13] in 5 cases Respirations

[13] Armanino and Ory Am Jour Med Sci, *211*, 597, 1946

are of the long, deep rapid Kussmaul ("air-hunger") type. The air-hunger may be replaced by shallow respiration when death approaches. The eyeballs are soft, the mouth and tongue are dry and present a dirty coating. At intervals the patient vomits dark brown material, obviously changed [illegible]

companying infection, is often below normal. The pulse is rapid and weak and the blood-pressure low. Often the muscles are flaccid, the tendon reflexes diminished or absent and the pupils dilated. Falta[14] states that the Loewi reaction (dilation of the pupil when a drop of epinephrine is applied to the eye) is often strongly positive.

In patients who have an infection such as pneumonia or phlebitis, the development of severe ketosis may reduce the temperature to subnormal, yet, within a few hours after the control of the ketosis, fever will return. The presence of fever in a ketotic patient usually indicates some infection. The tenderness and muscular spasm sometimes elicited upon palpation of the abdomen, together with leucocytosis and vomiting may lead to diagnostic difficulty. Tendon reflexes present on admission may disappear with the development of hypokalemia.

F. LABORATORY FINDINGS IN DIABETIC COMA

In the following discussion reference is made again to the summary, Table 64, which gives the average results in five series of coma cases treated thus far.

Blood Sugar. The average initial blood sugar varied surprisingly little from series to series being between 499 and 581 mg. per 100 cc. This [illegible]

the initial blood sugar [illegible]
Of these 34 recovered [illegible]
with recovery of the p[illegible]

If it is true that in diabetic coma the level of the blood sugar depends not merely upon food ingestion but upon the degree of excessive glucose formation from protein and fat as well as from glycogenolysis, then a relation exists between the severity of the metabolic disorder and the blood sugar level. In Table 67 the correlation of blood sugar levels and the insulin requirement in 302 cases indicates that this relationship should not be neglected.

Dillon and Dyer[15] reported 25 cases of diabetic coma in which the blood sugar was 1000 milligrams per cent or more on admission to the Philadelphia General Hospital. Of these 9 recovered and 16 died. Sixteen were women and 9 were men. The ages varied between twenty-one and fifty-nine years. Fourteen of the 25 patients were negroes. Recovery took place in a colored

[14] Falta. Loc. cit. p. 79.
[15] Dillon and Dyer. Ann. Int. Med., loc. cit. p. 351.

woman, aged twenty-one years who entered with a blood sugar of 1850 milligrams per cent, a plasma CO_2 combining power of 13 volumes per cent, and blood urea nitrogen of 95 milligrams per cent.

Blood CO_2, Ketones and Electrolytes (Sodium, Potassium and Phosphorus).—For discussion of these blood components in diabetic acidosis and coma, see page 378.

Blood Non-protein Nitrogen.—An elevation in the non-protein nitrogen content of the blood occurs frequently. Average values in the different groups have varied from 41 to 55 milligrams per cent in the initial blood samples Among the 165 cases in Series V, 55 or 33 per cent, had on admission a [illegible] these [illegible] the n[illegible] grams per cent.

Urine Findings.—The urine almost invariably contained on admission a large quantity of diacetic acid as shown by a definitely positive ferric chloride (Gerhardt) reaction Only in cases in which there is associated [illegible]

if these were cases of true diabetic coma. In case 25957 the urine gave no test for diacetic acid or acetone but the blood acetone content was 70 milligrams per 100 cc and the blood non-protein nitrogen was 63 milligrams

The amount of sugar in the urine varied on the average between 3 and 4 per cent, strikingly high values are rare and of good omen Values under 1 per cent may accompany failure of renal function. The urine usually gives a positive test for albumin and the astonishing showers of granular casts seen in the sediment are a classical and frequent finding.

Blood Chloride and Anuria.—The fact that the chloride of the blood plasma is frequently lowered has already been mentioned. It is noteworthy that urinary secretion may cease and retention of non-protein nitrogen with uremia may follow In 3 cases reported by Root[16] injections of 50 cc. to 130 cc of 10 per cent salt solution intravenously induced urination and relieved dangerous nitrogen retention This measure may succeed after patients have been given, without benefit, large amounts of physiological salt solution parenterally as well as hypertonic glucose solution intravenously, but the indication for such treatment is a low percentage of salt in the blood, it is possible that a diminution in the sodium rather than the *chloride content of the blood is the responsible factor, but data are* not complete on this point Krarup[17] has reported upon the successful use of 1 liter of 1 3 per cent sodium bicarbonate solution intravenously daily for three days in a patient who developed anuria and an elevated blood urea following diabetic coma In Krarup's patient the plasma chloride was normal but the alkali reserve was still low His case was therefore not comparable to those reported by Root

Hematologic Changes—Leukocytosis is the rule in coma and values from 15,000 to 50,000 white blood corpuscles per cubic millimeter are com-

[16] Root Jour Am Med Assn, *103*, 482, 1934, *108*, 947, 1937
[17] Krarup Ibid, *114*, 1604, 1940

monly found even though there be no accompanying infection The highest count in our series was 92,000, in Case 13074 Lawrence[19] has called attention to the increase in formed elements of the blood with a color index over

with-

and

11-

oxysteroids increased 2 to 8 times over normal controls This "alarm" reaction resulted in increased elaboration of steroid hormones and may well explain the absence of eosinophiles in coma

G THE DIFFERENTIAL DIAGNOSIS OF COMA

An unconscious patient always presents a problem in distinguishing promptly between various causes for coma When the patient is a known diabetic, the possibility of diabetic coma comes quickly to mind One must not, however, forget that acidosis and coma may be the first evidence of diabetes, particularly in small children, and the patient, therefore, may come to the physician's care without any knowledge on the part of the family that diabetes exists In Table 65 are summarized the chief points of differential diagnosis of hypoglycemia due to an insulin reaction and diabetic coma. At this point it should be remembered that simple starvation or excessive dehydration may produce acetonuria Unconsciousness due to diabetic ketosis and acidosis rarely occurs with the blood CO_2 combining power above 12 mm per liter unless some complicating factor such as infection or uremia is present

Hypoglycemia Due to Insulin Reaction. – Perhaps one of the most fatal errors in internal med

already has hypoglycemia

always, sweating or moist

terus A urine specimen immediately obtained by catheter should be sugar free but such urine may show sugar because it has been long in the bladder The onset of reactions due to protamine zinc insulin is usually more gradual than with regular insulin If the hypoglycemia is due to protamine zinc insulin, the patient may again develop hypoglycemia twenty or thirty minutes later and require giving of readily available carbohydrate by mouth, under the skin or by vein, which usually gives prompt relief When faced with the problems of unconsciousness in a diabetic patient at home or under conditions in which laboratory studies are difficult to carry out, it is justifiable to give a small amount of glucose in concentrated sterile solution intravenously If prompt and complete recovery takes place, then an insulin reaction was probably the presenting condition, if no improvement is noted in a very few minutes the condition may not be due to hypoglycemia and more exact study with hospitalization is indicated It should be emphasized that recovery following the giving of sufficient glucose (10 50 grams) intravenously should be prompt and definite if one is to assume that the condition is one of hypoglycemia Otherwise, labora-

[19] Lawrence Brit Med Jour 2 145 1932
[20] McArthur, Sprague and Mason Proc Am Diabetes Assn, 9 133, 1949

woman, aged twenty-one years who entered with a blood sugar of 1850 milligrams per cent, a plasma CO_2 combining power of 13 volumes per cent, and blood urea nitrogen of 95 milligrams per cent.

Blood CO_2, Ketones and Electrolytes (Sodium, Potassium and Phosphorus).– For discussion of these blood components in diabetic acidosis and coma, see page 378

Blood Non-protein Nitrogen.– An elevation in the non-protein nitrogen content of the blood occurs frequently. Average values in the different groups have varied from 41 to 55 milligrams per cent in the initial blood samples. Among the 165 cases in Series V, 55 or 33 per cent, had on admission a non-protein nitrogen value of 45 milligrams per cent or over. Of these 5 died but only 2 of the deaths were among the 5 patients in whom the non-protein nitrogen values were highest, 88 milligrams to 102 milligrams per cent.

Urine Findings. –The urine almost invariably contained on admission a large quantity of diacetic acid as shown by a definitely positive ferric chloride (Gerhardt) reaction Only in cases in which there is associated [illegible]

if these were cases of true diabetic coma In case 25037 the urine gave no test for diacetic acid or acetone but the blood acetone content was 70 milligrams per 100 cc and the blood non-protein nitrogen was 63 milligrams [illegible] between 3 and 4 [illegible] Values under [illegible] e urine usually gives a positive test for albumin and the astonishing showers of granular casts seen in the sediment are a classical and frequent finding

Blood Chloride and Anuria. The fact that the chloride of the blood plasma is frequently lowered has already been mentioned. It is noteworthy that urinary secretion may cease and retention of non-protein nitrogen with uremia may follow. In 3 cases reported by Root[16] injections of 50 cc to 130 cc. of 10 per cent salt solution intravenously induced urination and relieved dangerous nitrogen retention. This measure may succeed after patients have been given, without benefit, large amounts of physiological salt solution parenterally as well as hypertonic glucose solution intravenously, but the indication for such treatment is a low percentage of salt in the blood, it is possible that a diminution in the sodium rather than the chloride content of the blood is the responsible factor, but data are not complete on this point Krarup[17] has reported upon the successful use of 1 liter of 1 3 per cent sodium bicarbonate solution intravenously daily for three days in a patient who developed anuria and an elevated blood urea following diabetic coma In Krarup's patient the plasma chloride was normal but the alkali reserve was still low His case was therefore not com- [illegible]

[16] Root Jour Am Med Assn , *103*, 482, 1934, [illegible], 917, 1937.
[17] Krarup Ibid , *114*, 1601, 1940

spread tenderness and spasm are so suggestive of acidosis, without demonstrable intra-abdominal pathological changes, that operation should not be done unless the abdominal symptoms persist after three or four hours of adequate treatment with insulin. Conversely, a history of abdominal pain with or without vomiting, when associated with localized and definite

TABLE 65.—DIFFERENTIAL DIAGNOSIS IN HYPOGLYCEMIA AND DIABETIC COMA[1]

	*Hypoglycemia**	*Diabetic Coma*
History	Insufficient food, excess insulin, excess exercise	Insufficient insulin, infection, gastrointestinal upset
Onset	Following short-acting insulin: Suddenly, a few hours after injection Following long-acting insulin: Relatively slower, many hours after injection	Slow: hours or days
Course	Anxiety, sweating, hunger, headache, diplopia, incoordination, twitching, convulsions, coma (Headache, nausea and haziness especially following long-acting insulin)	Polyuria, polydipsia, anorexia, nausea, vomiting, labored deep breathing, weakness, drowsiness, possibly fever and abdominal pain, coma
Physical findings	Pale moist skin, full rapid pulse, dilated pupils, normal breathing, blood pressure normal or elevated, overactive reflexes, positive Babinski	Florid, dry skin, Kussmaul breathing with acetone odor, decreased blood pressure, weak rapid pulse, soft eyeballs
Laboratory findings	Second urine specimen sugar- and ketone-free, low blood sugar, normal serum CO_2	Urine contains sugar and ketone bodies, high blood sugar, low serum CO_2

*The features of an insulin reaction listed in this table are those observed after rapidly- [illegible] resemble more nearly those of regular insulin

[1] From Root and White: Diabetes Mellitus, New York, McGraw-Hill Book Co., p. 120, Table 18, 1956

abdominal tenderness, usually with spasm, is suggestive of a surgical lesion within the abdomen in the patient with diabetic acidosis, just as is the case in the non-diabetic patient, and may be an indication for immediate operation. In that rare case, in which definite differentiation is impossible and yet imperative, it may be safer to open the abdomen under local anesthesia than to suffer further delay.

II. THE TREATMENT OF DIABETIC COMA

Treatment Prior to Hospital Admission.—A patient in diabetic acidosis deserves to be in a hospital. By this means every facility is afforded

tory confirmation is imperative. In our own Case 2967, reported in detail elsewhere,[20] such improvement followed intravenous injections of glucose that doctors and nurses felt their original diagnosis of hypoglycemic coma was verified and yet the patient died two hours after admission to the hospital. Information from the laboratory, obtained too late to be of help, showed that the unconsciousness was that of profound diabetic coma in that end-stage in which Kussmaul respiration had given way to the pre- [illegible] continues without insulin. Be forehanded Always plan ahead as to how laboratory aids can be promptly secured.

Uremia. – The problem of differentiating uremia is becoming more frequent today as more diabetic patients are encountered, who, because of uncontrolled diabetes for many years, have reached the stage of diabetic nephropathy With nitrogen retention and uremia, nausea, vomiting, ketonuria and ketonemia may occur. The blood sugar level may exceed 500 mg. per cent and depression of the CO_2 content of the blood may be similar to that of diabetic ketosis In the diabetic patient who has uremia only but no real ketosis as shown by blood level for acetone, increased blood pressure and cardiac enlargement will be helpful In the patient who has both diabetic ketosis as shown by his history and the presence of large amounts of ketone in urine and blood serum, as well as renal failure indicated by *marked albuminuria and nitrogen retention, the problem* will require careful laboratory studies

Cerebro-vascular Accident. – The onset of unconsciousness has been relatively rapid although a history of severe headache during the days preceding unconsciousness may have been present Changes in reflexes, muscle tone or *muscle contour may be helpful The blood sugar may be* elevated and the spinal fluid may contain gross blood Little or no acetonuria or acetonemia is present

Toxicity from Other Causes. Toxicity from acute infection or from drugs such as barbitals may be confusing Marked salicylate poisoning resulted in stupor, Kussmaul respiration, dehydration and a strongly positive ferric chloride test due to the salicylate in a boy aged eighteen months described by Bowen, Roufa and Clinger [21] Brain tumor or meningitis may be recognized by means of reflex changes, a stiff neck and the Kernig's sign *and increased leucocytosis in the cerebrospinal fluid* Slow pulse and evidences of intracranial pressure in the eyegrounds direct attention to brain tumor

Dr L S McKittrick,[22] our surgical colleague, who sees in consultation many of our coma cases, has discussed from the surgical viewpoint the *differential diagnosis and treatment of a diabetic patient with nausea,* vomiting and abdominal pain *He states that in a diabetic, malaise,* drowsiness, vomiting and diffuse abdominal pain associated with wide-

[21] Bowen, Roufa and Clinger Jour Am Med Assn, *107*, 276, 1936
[20] Joslin *et al* Arch Int Med, *59*, 175, 1937
[22] McKittrick *New England Jour Med*, *209*, 1033, 1933

15 [illegible]

SIXTH TO TWENTY-FOURTH [illegible]

If test is—	Red	Orange	Yellow	Green	Blue	
Give—	20	16	12	0	0	units

17 [illegible]

18 Sudden onset of muscular weakness, or loss of tendon reflexes, and shallow respiration suggest hypokalemia Potassium may be given P O or I V, if changes in ECG or in serum potassium are present

SECOND DAY AND SUCCEEDING DAYS

19 Soft Food—Diet carbohydrate 100 to 150 gms, protein 50 gms, fat 50 gms Gradually return to standard diabetic diet for age and weight with carbohydrate 150 to 200 gms, protein 60 to 100 gms, fat 60 to 120 gms daily

ADDITIONAL NOTES

I [illegible]

TOTAL KETONES IN BLOOD

	Mg Per 100 cc
Normal	0 to 5
Non-Diabetic Uremia	5 to 60
Diabetic Coma	50 to 200+

II [illegible]

TABLE 66.—TREATMENT OF DIABETIC ACIDOSIS AND COMA[1]

Joslin Clinic, New England Deaconess Hospital

FIRST HOUR AFTER ADMISSION. Special nurse, preferably experienced in coma treatment, for the first few hours

LABORATORY

1 *Urine* Examine for sugar, acetone, diacetic acid, albumin, coma casts and pyuria Catheterize if necessary
2 *Blood* Test for sugar, CO_2 content and non-protein nitrogen, with emergency report within an hour White blood count Serum potassium if indicated Hematocrit as aid in assessing dehydration.

CLINICAL

[illegible] rate, blood pressure, and

(b) *Look for soft eyeballs, dry tongue, dilated stomach, cold and mottled skin, impacted rectum, and tendon reflexes*
C X-ray chest and abdomen when possible
D ECG (a) coronary (b) potassium changes

[illegible]

5 *Gastric Lavage* Aspirate completely and wash stomach with warm water with greatest care
6 Normal saline intravenously, 2000 cc It is desirable to change to a solution of [illegible]

7 [illegible]

SECOND TO SIXTH HOUR. *The gravity of the case may require repetition of first hour's total insulin in the second hour*

8 Give potassium solutions by vein for definite indications (a) when blood analysis or ECG clearly indicates hypokalemia (b) when potassium depletion is probably present as result of prolonged serious ketosis and or deficient potassium intake (c) only in the presence of adequate urinary output, 25 meq K per hour up to 100 meq may be given
9 Repeat blood sugar and CO_2 determinations after three or four hours For rising blood sugar give insulin hourly 50 200 units or more, according to estimate of prognosis
10 [illegible] resume
11 [illegible]
12 [illegible] re hourly Con-
13 [illegible] output as index
14 [illegible] vein frequently needed

[1] From. Root and White Diabetes Mellitus, New York, McGraw-Hill Book Co., p 124, Table 19, 1956

because of the greater speed of action thus obtained In Table 67 it is evident that from one-half to two-thirds of the total twenty-four hour

with blood sugar values between 1300 and 1600 mg per 100 cc., an average of 611 units insulin was given in the first three hours In 52 cases treated between 1923 and February, 1927, the average amount of insulin given in the first three hours was 83 units Deaths occurred in 18 per cent. In 302

acidosis advances It is the insulin given in the first few hours which counts most heavily

TABLE 67 —BLOOD SUGAR LEVEL CORRELATED WITH INSULIN DOSE IN 302 COMA CASES

Admission Blood Sugar Mg /100 cc	*Cases*	*Average Insulin First 3 Hours Units*	*Average Insulin First 24 Hours Units*
2250	1	325	1125
1300–1600	6	611	1173
1000–1300	16	460	760
600–1000	82	325	509
400–600	108	187	284
200–400	84	108	152
100–200*	5	62	128

*Low values due to insulin given en route to hospital

The urgency of rapidly giving large doses of insulin in the first three hours rests upon the necessity of controlling polyuria and glycosuria Therefore, the more rapidly the blood sugar can be reduced toward normal the more

sequent intracellular dehydration

A dose of insulin similar in size to the initial dose may be given every half-hour until there is clinical and chemical evidence of improvement Then urine specimens are secured at intervals of one or two hours with instructions to give insulin according to the Benedict's test, for example, 20 units for a red or orange test, 15 for a yellow, and 10 for a yellow-green test This dosage, too, must be varied depending on the severity of the acidosis, the age of the patient, and the response to treatment Unless forced to do so, we prefer not to catheterize patients, for fear of resulting infection Instead we make frequent blood-sugar estimations (capillary

Ed extbook of Endocrinology, 2nd

Thomas, 1955

, (in press) 1958

because of the greater speed of action thus obtained In Table 67 it is evident that from one-half to two-thirds of the total twenty-four hour amount of insulin required was given in the first three hours. In Case 8035, female, age 42 years, the blood sugar value of 2250 mg was confirmed by a second analysis We gave only 325 units in the first 3 hours In 6 cases [illegible] average [illegible] treated [illegible] given in [illegible] In 302 cases from January, 1946 to July 1, 1956, the average dose of insulin in the first three hours was 224 units, and only 5 deaths occurred, or 3 0 per cent Actually, additional insulin was given on telephone order before admission in amounts varying from 20 to 100 units Insulin resistance increases as acidosis advances It is the insulin given in the first few hours which counts most heavily

TABLE 67 — BLOOD SUGAR LEVEL CORRELATED WITH INSULIN DOSE IN 302 COMA CASES

Admission Blood Sugar Mg /100 cc	*Cases*	*Average Insulin First 3 Hours Units*	*Average Insulin First 24 Hours Units*
2250	1	325	1125
1300–1600	6	611	1173
1000–1300	16	460	760
600–1000	82	325	509
400–600	108	187	284
200–400	84	108	152
100–200*	5	62	128

*Low values due to insulin given en route to hospital

The urgency of rapidly giving large doses of insulin in the first three hours rests upon the necessity of controlling polyuria and glycosuria Therefore, the more rapidly the blood [illegible]

[illegible]

Then urine specimens are secured at intervals of one or two hours with instructions to give insulin according to the Benedict's test, for example, 20 units for a red or orange test, 15 for a yellow, and 10 for a yellow-green test This dosage, too, must be varied depending on the severity of the acidosis, the age of the patient, and the response to treatment Unless forced to do so, we prefer not to catheterize patients, for fear of resulting infection Instead we make frequent blood-sugar estimations (capillary

[23] Forsham and Thorn The Pancreas, in Williams Textbook of Endocrinology, 2nd Ed, Philadelphia, W B Saunders Co, p 459, 1955
[24] Ricketts Diabetes Mellitus, Springfield, Ill, C C Thomas, 1955
[25] Colwell Diabetes, 2, 262, 1953, Arch Int Med, (in press) 1958

Table 66.—*Continued.*

III Electrolyte-containing solutions. Potassium should not be given intravenously in excess of 25 mEq per hour!! Rarely is it wise to exceed 100 mEq in 12 hours unless definite hypopotassemia is present and urine secretion is ample. After 12 to 24 hours if 3 to 4 grams potassium cannot be taken by the patient in diabetic diet, a simple solution may be taken in divided amounts. Thus, two hundred cc. orange juice plus 2 grams potassium phosphate may be diluted with water to 500 cc. Of this give 100 cc. per hour. With fall in blood sugar and need for potassium, a 5 cc. ampule (2 grams dibasic potassium phosphate and 0.4 grams monobasic potassium phosphate) may be added to 1,000 cc. of 5 per cent glucose for intravenous administration if indicated.

IV Electrocardiographic signs of

A Low serum potassium (below 3.0 mEq).
1 Lowered or inverted T waves
2 Depressed ST segments
3 Lengthened QT, or appearance of U wave.
4 Prolonged P-R interval

B High serum potassium (above 6.0 mEq)
1 High, peaked T waves
2 Wide QRS
3 Disappearance of P waves
4 AV dissociation
5 Final disorganization of ECG

Note A normal ECG does not exclude K deficiency. The above changes may not always be due to hypokalemia.

for constant observation with uninterrupted treatment, including the administration of parenteral fluids, and as frequent analyses of the blood and urine as may be necessary. If one learns by telephone that a patient at home is to be brought to the hospital, a preliminary dose of 20 to 40 units of insulin given by the home physician or the family may be advised provided the diagnosis seems certain. Actually doses ranging from 50 to 200 units have been given prior to admission. A bed at the hospital should be prepared and necessary equipment as blankets, hot-water bottles, stomach and rectal tubes, salt and glucose solutions, insulin, and stimulants assembled so that when the patient arrives, treatment begins. A portable diabetic treatment stand equipped with materials for giving prompt intravenous injections, catheterization, etc., should prevent delay. A laboratory technician should be instantly available and continuously so until the patient is out of danger so that no time is lost in getting reports. In Table 66 is summarized in outline the plan of treatment which we have found useful at the New England Deaconess Hospital.

Insulin. On admission, after the diagnosis has been verified by history, physical examination and examination of the urine, a preliminary subcutaneous dose of insulin usually of 50 to 100 units is given. This dose must be varied to suit the age of the patient, the degree of acidosis, and previous insulin administration. The insulin should be of the unmodified, "regular" or crystalline type; protamine zinc insulin acts so slowly that it should not be used except as an adjunct to treatment with the other varieties.

The chief objective in this first few hours of treatment is to give as much insulin as is needed.[23–25] Usually 50 or more units are given intravenously

tient is anuric without infections or other causes (see page 371) then maximal dehydration may be assumed If no other cause but diabetic acidosis explains the anuria relief has occasionally occurred with the administration of as much as 1 liter of salt solution per hour In the two patients reported by Root and Riseman[32] not only were large quantities of insulin necessary but extraordinarily large amounts of fluid were given In one anuric patient 13,800 cc and the other 11,000 cc of total fluid were

in shock, and with acidosis of long duration, special consideration and definition of the probable losses sustained by the patient indicates the use of other solutions For discussion of electrolytes, see page 378

During the first few hours of treatment of coma obviously no glucose solution should be given, since it may have an undesirable effect in con-

formed Glycogen is deposited with about 0 36 millimols potassium[34] per gram of glycogen Using Soskin's est

per kilogram body weight a 70 kg ma

cogen during treatment and recovery

millimols potassium from the serum

Perry and Rosenbaum [37] Values for serum potassium below the normal range of 3 0 to 5 1 mEq occur in diabetic acidosis,[38] but particularly have been reported at the end of twelve to twenty-four hours of treatment when the blood sugar values and CO_2 values have approached normal One of the three hazards in treating diabetic coma discussed by Root, Story and Cortesi,[39] is the danger of inducing hypokalemia if glucose solution is given particularly during the full activity of insulin when the level of glucose in the blood is falling rapidly In one case described by Perry and Rosenbaum 3000 cc of 5 per cent glucose solution were given during a five-hour period when the blood sugar value had begun to fall rapidly Death occurred four hours later with a serum potassium value of 1 07 mEq It seems clear that the administration of glucose solution in quantities far in excess of the possibility of oxidation when a large dose of insulin

[32] Root and Riseman Jour Am Med Assn 110 1730 1938

[33] Howard, D

[34] Darrow

[35] Martin an Proc

Am Diab Assn , *147*, 24, 1951

blood may be conveniently used) as a guide to treatment if urine specimens cannot be secured

In patients long in coma, and especially in the presence of severe complications such as myocardial infarction, insulin has been required in doses of several thousand units in 24 hours. The presence of an insulin antagonist in the serum of patients in diabetic coma has been demonstrated by Field, Tietze, and Stetten[26] in such concentration as might neutralize or inhibit the effect of large amounts of insulin It was capable of inhibiting human insulin.

If the patient is in circulatory collapse, so that doubt exists about the [illegible] it intravenously as well as subcutane- [illegible] sorption, intravenous administration [illegible] pronounced, though less prolonged, hypoglycemic effect than subcutaneous injection.

A patient may rarely pass from diabetic coma into the unconsciousness which attends hypoglycemia without striking, warning signs and such a possibility one should always remember This is explainable on the as- [illegible]

test is green or blue and as a further precaution, frequent determinations of the blood sugar are advisable at this stage of treatment

Fluids. Dehydration and loss of electrolytes are two of the most important clinical features of diabetic coma The skin is dry and inelastic, the tongue and mucous membranes of the mouth are parched, the eyeballs are soft, and the subcutaneous tissues are obviously depleted of fluid.

It was shown soon after the use of insulin began that in advanced diabetic coma insulin alone was not sufficient to restore the patient to normal The dehydration and starvation of severe diabetic coma resulted in losses of electrolytes which exceeded the catabolism of tissue represented by nitrogen loss[29-31]

The primary aim in rapid treatment of diabetic coma with insulin and fluids is to make possible a restoration of normal feeding as soon as possible The restoration of fluid and electrolytes is most readily begun by the prompt in [illegible] solution w [illegible] When the [illegible] subcutane [illegible] of the heart to follow even liberal quantities of salt solution if a reasonable estimate of the degree of dehydration has been correct.

Actual determination of the degree of dehydration is difficult If a pa-

[26] Field, Tietze and Stetten Jour Clin Invest, *36*, 1588, 1957 Field Diabetes, *7*, 433, 1958
[27] Best Jour Am Med Assn, *105*, 270, 1935
[28] Atchley, Loeb, Richards, Benedict and Driscoll Jour Clin Investigation *12*, 297, 1933
[29] Butler, Talbot, Burnett, Stanbury and MacLachlan Tr Assn Am Physicians, *60*, 102, 1947
[30] Butler Acta paediat, *38*, 59, 1949
[31] MacArthur, Harting, Smart and Talbot Jour Clin Invest, *29*, 832, 1950

ment he gives 0.3 to 0.4 milligrams of strophanthin intravenously. In extreme failure of the circulation he recommends the addition of sympatol or adrenalin to a constant intravenous drip in amount of 1 to 2.5 cc. of a 1 to 1000 solution hourly, following the blood-pressure all the while. Though by no means deprecating the use of drugs, we must reiterate that we have encountered no case in which such medication has appeared to be lifesaving

Blood Transfusions.—Blood transfusion has been carried out with relatively few of our patients There have been occasional transfusions in selected cases but it has always been extremely difficult to evaluate the effect, and to know whether the benefits obtained were due to the trans-

judging their value be had So often the need for unusual measures is not, or cannot be, appreciated until the patient has been in the hospital a few hours and the lack of satisfactory response to treatment noted

Glucose and Food.—The question of the use of glucose or fructose depends upon the period in the treatment of diabetic coma which is under discussion The treatment of diabetic acidosis or coma may be divided into two periods: (1) The first 3-5 hours after admission of the patient in severe diabetic ketosis, when marked hyperglycemia and dehydration are present This period may be short, even as little as two hours, in children or patients with diabetes of short duration, but it may be more than five

original level It is in this second period when we have always, since the introduction of insulin thirty years ago, favored the use of carbohydrate

and especially to prevent or treat hypoglycemia, resulting from insulin action, if it occurs

tion It is clear that the utilization of glucose from glycogen is, although not an important item, facilitated by the improvement in glucose utilization within the cell

tant item dur

solution to a

1000 mg. per

circumstances does produce an increase in intracellular glucose utili

is effective may well result in such a rapid transfer of potassium from the serum as would explain death under these circumstances. Reported deaths in hypokalemia have most commonly occurred at periods from twelve to eighteen hours after the initiation of treatment with large doses of insulin and glucose solution. At the New England Deaconess Hospital we have [illegible]

had declined. *So far although we have seen serum potassium levels at the initiation of treatment of 5 mEq. fall to 3 mEq. during the course of twelve or fifteen hours we have not yet seen clinical hypokalemia developing during the course of treatment.* On the other hand spontaneous hyperkalemia has occurred in one patient suffering from diabetic nephropathy and severe uremic acidosis as renal failure came on

All solutions should be slightly above body temperature, should be given slowly, and with great caution to avoid infection or unnecessary trauma Following a cleansing enema, salt solution may at times be given rectally with success. This must be done with care. Bertram[40] mentions a patient in whom sepsis developed following intestinal necrosis at the site of insertion of a rectal tube. Avoid pressure from hot water bottles since slight pressure during coma may result in gangrene as occurred in two adolescent diabetic patients reported by Whittaker.[41] After gastric lavage, fluids as broths, orange juice or ginger ale may be given cautiously by mouth. Usually it is preferable to wait perhaps an hour after gastric lavage and then begin by limiting such fluids to 100 cc per hour Although the treatment of dehydration and shock is of great importance, remember that uncontrolled diabetes is the cause of coma Give enough insulin early!

Gastric Lavage. Gastric lavage should be carried out routinely unless the patient is *in extremis* or in such condition that the procedure involved would be dangerous Usually one's efforts will be rewarded by finding the stomach filled with sizable quantities of fluid, food remains and old blood Removal of such contents and gentle lavage with warm water or normal salt solution relieves the abdominal distress, stops vomiting, and prepares the way for the early administration of fluids by mouth

Circulatory Stimulants. Circulatory stimulants are practically never needed with children and in adults rarely produce startling or lasting results Epinephrine in doses of 0 3 to 1 cc may be given subcutaneously for extreme collapse Ephedrine sulphate gives a more prolonged effect in raising blood-pressure and may be given subcutaneously in doses of 0.5 to 1 cc (25 to 50 mg) Either epinephrine or ephedrine may be given intravenously in emergencies but usually if the situation is grave enough to warrant such medication, the prognosis is bad Norepinephrin (levofed) is effective but dangerous

The previous statement has been questioned by Bertram, who believes that energetic support of the circulation is necessary in order to counteract the development of cardio-vascular collapse. Accordingly, early in treat-

[40] Bertram P 81 Loc cit, p 350
[41] Whittaker Brit Med Jour, 2, 469, 1944

or oatmeal gruel may be given in amounts furnishing 10 grams carbohydrate per hour beginning as early as the sixth or eighth hour after admission In unconscious patients intravenous administration of glucose is necessary for the first few days

Arguments advanced for the use of fructose or invert sugar include the [illegible] the aid of insulin than with glucose. [illegible] nall portion of the fructose escapes conversion to glucose

At present it may be said that few, if any, clinics with a large experience with the treatment of diabetic ketosis and coma both in adult and in childhood diabetes, now employ the use of glucose solutions intravenously during the first few hours of the treatment of severe diabetic ketosis

Vitamins and Antibiotics.—Several factors of the vitamin B-complex (thiamine, riboflavin, and niacin) are essential to the enzyme systems in- [illegible]

[illegible]

with 10 cases of diabetic coma to whom they gave cocarboxylase The CO_2 of the blood rose to 40 in seven hours in the control series and only required 4 3 hours in the treated series The elevated pyruvic acid level was reduced In the New England Deaconess Hospital cases no better results were obtained in the cases to whom cocarboxylase was given than in other coma cases

Gilliland and Wartin[47] treated 10 [illegible]

[illegible]

covery, lowering of the raised level of blood pyruvic acid, the blood sugar, [illegible]

Cleansing Enema.—A cleansing enema is routinely given to relieve abdominal distention and promote intestinal tone

[46] Boulin, Uhry, Meyer and Bonfils Presse Médicale, *57*, 689, 1949
[47] Gilliland Brit Med Jour, *1*, 916, 1951

The depletion of sodium chloride has been recognized as a major factor, especially in shock, and ever since 1923

sugar rises, the effective osmotic pressure of the extracellular fluid increases A striking demonstr of giving gl

given moderate

in 20

grave in one case with anuria, following the administration of glucose, plasma concentration of sodium and of chloride fell rapidly. This was interpreted to mean a withdrawal of water from cells and a corresponding dilution of plasma. Increasing intracellular dehydration by the giving of glucose solution in the early hours of treatment of coma is one of its worst features, well illustrated in a series of cases reported by Lee, Naidoo and Torrens.[43] In 14 cases they used glucose solution in the early hours and in another 14 cases quite comparable in severity, blood chemistry and other details, they used only saline solution. The mortality was 4 times greater in the glucose treated group

Recently, Cahill, Ashmore, Earle and Zott

rena

Hav Peters.[45 46]

Serial determinations of the blood sugar afford an excellent guide to treatment during the first several hours in the hospital. Obviously such values are robbed of their significance if a constant infusion of glucose is being carried out.

When glucose is given at a rate exceeding caloric needs, such as 100 to 400 grams within a few hours, a considerable portion of this gl

excess g

may res

[42] Seldin and Tarail Jour

[43] Lee, Naid

[44] Cahill, As

[45] Peters, M

[46] Ross, McG 1956

[47] Drury Am Jour Physiol, *131*, 536, 1940

[48] Pauls and Drury Jour Biol Chem, *145*, 481, 1942

Circulatory Collapse.—Because of its importance, a further word may well be said regarding the treatment of profound shock characterized by a blood-pressure below 90 mm of mercury (at other times too low to measure), rapid pulse, and eventual anuria This state is not limited to older patients and may be seen in advanced coma at any age One must agree with Lande[53] regarding the poor prognosis which attends such a case. On the other hand, we have seen unexpected recovery in a pulseless patient aged seventy years, treated with the methods outlined above Cases 6803, 7047 and 10970 had blood-pressures from 0 to 80 mm Hg but made good recoveries We continue to use normal salt solution with lactate in amounts from 3 to 5 or more liters administered subcutaneously and intravenously in addition to fluids by mouth and rectum When indicated this is supplemented by adrenalin or ephedrine subcutaneously or intravenously For anuria accompanied by a subnormal plasma chloride we use 10 per cent salt solution in 60 cc quantities as described on page 361. The use of transfusions of whole blood may be helpful in cases with blood pressure under 70 mm of mercury

Anuria or Oliguria—Suppression of urine is an ominous complication of ketosis or coma Each of the following causes has been observed in one or more of our coma cases

(*a*) Dehydration, loss of plasma and circulatory collapse, the most frequent

(*b*) Shock from burns, trauma or tissue necrosis.

(*c*) Poisoning and allergic reactions to such drugs as sulfonamides or mercury

(*d*) Acute glomerulonephritis.

(*e*) Acute renal injury as in necrotizing papillitis, arterial thromboses, or the hepato-renal syndrome[54]

(*f*) Congenital absence of kidney

(*g*) Obstruction from stones, sulfonamide crystals or tumor.

(*h*) Acute renal shut-down, a rare event occurring even in early ketosis

Treatment is aimed to protect renal tissue and to avoid pulmonary edema or potassium retention by giving intravenous glucose solution (20–40 per cent in water) 750 cc to 1200 cc per 24 hours Anuria enduring for many days may terminate in recovery Hemodialysis, with the disposable coil artificial kidney, was employed successfully by Aoyama and Kolff[55] in treating a young woman in the seventh day of anuria following severe diabetic coma The blood urea content, at first 117 but later 171 mg per 100/ml, was reduced to 48 in six hours

J THE PROGNOSIS IN DIABETIC COMA

Important factors in the prognosis of diabetic coma are (1) the severity of the acidosis, (2) the duration and degree of unconsciousness before the institution of treatment, (3) the age of the patient, (4) the cardio-vascular-renal status of the patient, (5) complicating conditions, which are often

[53] Lande Jour Am Med Assn, *101*, 9, 1933
[54] Root New England Jour Med, *212*, 545, 1935
[55] Aoyama and Kolff Jour Am Med Assn, *166*, 9, 1958

Alkalies.—Experience has amply shown that in most cases alkalies are needless and if given in large quantities may be actually harmful. The danger of the use of soda has been fully discussed in previous publications. Kydd[48] has lent support to the opinion that without alkalies, treatment with insulin, fluids, sodium chloride, and carbohydrate suffices to provide for recovery from diabetic acidosis and eventual restoration of the body electrolytes. Falta[49] states that in recent years he has almost always carried out treatment without alkalies. He mentions that alkaline solutions given intravenously may check diuresis and lead to insulin edema.

Hartmann,[50] Guest[51] and Butler[52] recommend the use of sodium lactate in diabetic coma to hasten recovery from acidosis.

Treatment in Convalescence.—Following recovery from acute acidosis, return to normal is usually steady and rapid except in patients [illegible] and in severe shock. [illegible] on the day after admission the [illegible]

[illegible]

Within two or three days he is well on the way toward a regular maintenance diet. Indeed, improvement in general condition is often so rapid that one is apt to forget that the patient has suffered a terrific bodily insult from which prompt restitution to normal physiology and chemistry must be more apparent than real. Activity for a few days should be limited and a gradual return to a normal life insisted upon. An occasional complication is the appearance of edema of the extremities due to overcompensation in the matter of fluid retention.

I. COMPLICATIONS OF DIABETIC COMA

Any complicating condition may alter materially the prognosis in a given case of coma. Space does not permit mention of many interesting and instructive cases in this regard. However, it seems worth while to discuss briefly certain incidents which may occur in the course of the treatment.

Hypoglycemia.—Occasionally treatment may be so energetic that the blood sugar may be forced to hypoglycemic levels. It has already been mentioned that the patient can pass from diabetic coma to insulin shock without any striking sign of such an occurrence. Hence fairly frequent blood-sugar estimations are a valuable aid in treatment. Possibly because it is our invariable rule to begin to give frequent and small amounts of carbohydrate by mouth as soon as tolerated by the patient, we have never seen hypoglycemia following recovery from diabetic coma which gave rise to any serious difficulty.

The Return to a Condition of Coma After Apparent Recovery.—Such [illegible] does occur [illegible] ore [illegible] ion [illegible] of the patient and as frequent laboratory tests as are necessary.

[48] Kydd. Jour. Clin. Invest., *12*, 1169, 1933.
[49] Falta. P. 279, Loc. cit., p. 355.
[50] Hartmann. Arch. Int. Med., *56*, 413, 1935.
[51] Guest. Am. Jour. Med., 7, 630, 1949.
[52] Butler. Acta Paediat., 38, 59, 1949.

circulatory collapse—all *may* get well with proper treatment. It is usually a combination of adverse influences which is disastrous It is the complete situation in any individual case which is important in prognosis

Duration and Degree of Unconsciousness.—The duration of unconsciousness *before treatment is begun is of much importance in prognosis* It has been said by *some that if a patient is unconscious for eight hours*, by others twelve hours, that the outlook is grave. It is difficult to speak

effect upon the respiratory center

The determination of unconsciousness is not as easy as it would appear at first glance. A patient may be so stuporous and his mentality so clouded that he may be difficult to arouse and later, after recovery, not recall important incidents and yet at the time may respond to questions or to painful stimuli Accordingly, certain arbitrary standards must be set up.

Patients may be classified as *drowsy, semi-conscious, unconscious* but respond to pain, and completely unconscious Pain is elicited by touching the conjunctivæ

The degree of unconsciousness is certainly an important factor in the

in Case 23974 in whom recovery from unconsciousness occurred despite bilateral progressive pneumonia, anuria, and marked nitrogen retention. He received 1300 units during the first five hours of treatment.

Age of Patient—The age of the patient is a third important factor in prognosis Youth carries with it a great advantage Among 945 instances of coma in our entire series 225 occurred in 208 patients under fifteen years of age at the time of the attack of coma. Of these, there has been only one death and that was in a girl (Case 9162) fourteen years of age with diabetes of 3 8 years' duration who entered the hospital in a moribund state after

responsible for the precipitation of the acidosis; (6) grossly abnormal laboratory findings.

Factors of prognostic importance in moderate or severe diabetic acidosis were evaluated by Zieve and Hill[64] in 24 coma cases. Considered individually the order of effectiveness of significant prognostic variables were age, blood pressure, [illegible] least significance was the degree of unconsciousness.

Severity of Acidosis.—Naturally, those cases in which acidosis is most severe warrant a less favorable prognosis. This in itself is by no means a safe guide, however. Among 804 cases there have been 90 with a plasma CO_2 combinging power, or content, of 2.3 mm. per liter or less, and of these 78 recovered. There were 18 cases with a value of 1 mm. per liter and even of these 14 recovered. Furthermore, 21 of our fatal cases had a plasma CO_2 value of 7 mm. per liter or more on admission. A more important point is the character of the response to energetic treatment with insulin, fluids and appropriate electrolytes.

However, it is instructive to note that in our own series of cases there has been some correlation between the CO_2 value and mortality. This is shown in Table 68. Of 87 patients with lower CO_2 values 4.6 per cent died whereas

TABLE 68. MENTAL CONDITION AND PLASMA CO_2 VS. MORTALITY IN DIABETIC COMA

Jan. 1, 1940–July 1, 1951*

	Plasma CO_2 4.5 m. M. per Liter or Below		Plasma CO_2 5.0–9.0 m. M. per liter		Total cases	
Mental Condition	No. of Cases	Mortality Per Cent	No. of Cases	Mortality Per Cent	No. of Cases	Mortality Per Cent
Conscious	6	0.0	47	2.0	53	1.9
Drowsy or semi-conscious	49	7.0	168	1.2	217	1.4
Unconscious	32	10.0	36	11.0	68	10.3
Totals and averages	87	4.6	251	2.4	338	2.9

* Three cases with incomplete data have been excluded.

only 2.4 per cent of 251 patients with CO_2 values between 5.0 and 9.0 mm. per liter died. It is true that among the unconscious patients the percentage of deaths was essentially the same in the group with a CO_2 value above 10 volumes per cent as in the group with low values. In the latter series the number of deaths is too low for statistical comparison.

It cannot be too strongly emphasized that no single factor is all-important in prognosis. Patients with extreme acidosis, patients with marked hyperglycemia, elderly patients, patients unconscious for hours, and patients in

64 Zieve and Hill, Loc. cit., p. 350

Patients with preexisting nephritis, however, have a definite handicap In most patients the elevation of the non-protein nitrogen, together with the albuminuria and cylindruria are indications simply of temporary renal impairment, reversible in nature Bertram[59] believes the outlook to be bad when the total acetone content of the blood (acetone + diacetic acid, but not including β-oxybutyric acid) is greater than 70 milligrams per cent He regards the level of β-oxybutyric acid alone as of no significance, a point consistent with the fact as mentioned by Best and Taylor[60] that β-oxybutryic acid is a relatively non-toxic product as contrasted with diacetic (aceto-acetic) acid which probably derives toxicity from the enolic form, $CH_3COHCHCOOH$ The amount of β-oxybutyric acid formed by a diabetic in acidosis during twenty-four hours is far more than is realized. Thirty to 40 grams of total ketone bodies per day are not uncommon in precomatose stages[61] Case 4 once held a world's record for acid pro-

We have had no experience with determinations of the freezing point of the serum, but Bertram regards a depression of 0 68° or below as indicative of marked retention of ketone bodies and therefore of doubtful prognosis

The leucocytosis which is so characteristic of diabetic coma is of little value in prognosis It is best explained by the animal experiments of Tullis,[63] in which intense dehydration was followed by leucocytosis proportional to the degree of hemoconcentration Bertram has carried out determinations of the blood sedimentation rate and finds this value of no practical meaning

K THE MORTALITY AND CAUSES OF DEATH IN DIABETIC COMA

In the right-most column of Table 64 is given the mortality of the 5 groups of cases It has varied from 3 to 15 per cent Among the 969 coma admissions in 719 patients in the entire series there has been a total of 74 fatal cases, a case mortality of 7 6 per cent

From May, 1923, to January 1, 1937, there have been 1450 deaths among diabetic patients under our care at the New England Deaconess Hospital, 74 of these patients, or 5 1 per cent, entered in diabetic coma In Table 70 the fatal cases are listed by years The causes of death in these cases are

attacks of coma in 704 patients A total of 177 patients who had coma prior

[59] Bertram Loc cit, p 350
[60] Best and Taylor P 574, Loc cit, p 165
[61] Falta P 101, Loc cit, p 79
[62] Joslin Jour Med Res, *6*, 306, 1901
[63] Tullis Am Jour Med Sci, *215*, 424, 1948

years of age at the time of coma, one finds that there have been but 8 deaths *among 305 instances of coma. This case mortality of 2.6 per cent contrasts* sharply with that of 15.3 per cent among patients twenty years of age or older and 28.7 per cent in 80 patients in the 6th decade of life. Tautologous was the word applied by Peck and Peck[47] to a girl, aged 20 years, who had fifty repetitive instances of severe diabetic coma in 8 years. She was the product of a broken home and the attacks of coma appeared to be her own reaction to a most unpleasant, stressful situation at home.

Cardiovascular Status.—A fourth factor in prognosis which is in large measure influenced by each of the preceding two points, is the state of the cardiovascular system. Circulatory collapse which fails to respond to supportive treatment is seen almost exclusively in adult patients, because gross neglect is required to produce such a situation in a child. With adult patients a blood pressure which is subnormal (below 90 millimeters mercury) and with treatment fails to rise or continues to fall, signifies a grave prognosis. In patients with previously normal cardiac function, irregularities of the pulse may be a bad sign. With circulatory collapse [illegible]

rise in the carbon dioxide combining power of the blood plasma, but the blood non-protein nitrogen rises and the patient's clinical condition grows progressively worse.

Complications.—When diabetic coma is complicated by some other acute condition, the prognosis is, of course, determined by the nature and severity of the complication. It is significant and indeed encouraging that as years go by, deaths from diabetic coma occur for the most part in patients with serious complications, in themselves carrying a high mortality apart from the diabetic acidosis. Needless to add, the treatment of complications, particularly infections, including pneumonia, should be modern and energetic, full use of the newer chemotherapeutic agents should be made.

The presence of diabetic nephropathy (Kimmelstiel-Wilson) greatly increases the hazard of diabetic ketosis. Zubrod, Eversole and Dana[48] point *out that the development of ketosis is relatively infrequent in patients* with Kimmelstiel-Wilson lesions. Among 41 cases with Kimmelstiel-Wilson lesions 40 did not have at any time any ketosis. On the other hand within a year two young women at the New England Deaconess Hospital have shown on one admission severe ketosis and on another admission uremic acidosis from which each died.

Laboratory Data.—In estimating the prognosis in any given case the clinical condition of the patient and his response to treatment must be accorded greater weight than abnormal values obtained in laboratory [illegible]

[47] Peck and Peck. Diabetes, *5*, 44, 1956.
[48] Zubrod, Eversole and Dana. New England Jour. Med., *245*, 14, 518, 1951.

Patients with preexisting nephritis, however, have a definite handicap. In most patients the elevation of the non-protein nitrogen, together with the albuminuria and cylindruria are indications simply of temporary renal impairment, reversible in nature Bertram[59] believes the outlook to be bad when the total acetone content of the blood (acetone + diacetic acid, but not including β-oxybutyric acid) is greater than 70 milligrams per cent. He regards the level of β-oxybutyric acid alone as of no significance, a point consistent with the fact as mentioned by Best and Taylor[60] that β-oxybutryic acid is a relatively non-toxic product as contrasted with diacetic (aceto-acetic) acid which probably derives toxicity from the enolic form, $CH_3COHCHCOOH$. The amount of β-oxybutyric acid formed by a diabetic in acidosis during twenty-four hours is far more than is realized Thirty to 40 grams of total ketone bodies per day are not uncommon in precomatose stages[61] Case 4 once held a world's record for acid pro- [illegible]

We have had no experience with determinations of the freezing point of the serum, but Bertram regards a depression of 0 68° or below as indicative of marked retention of ketone bodies and therefore of doubtful prognosis

The leucocytosis which is so characteristic of diabetic coma is of little value in prognosis It is best explained by the animal experiments of Tullis,[63] in which intense dehydration was followed by leucocytosis proportional to the degree of hemoconcentration Bertram has carried out determinations of the blood sedimentation rate and finds this value of no practical meaning

K THE MORTALITY AND CAUSES OF DEATH IN DIABETIC COMA

In the right-most column of Table 64 is given the mortality of the 5 groups of cases It has varied from 3 to 15 per cent Among the 969 coma admissions in 719 patients in the entire series there has been a total of 74 fatal cases, a case mortality of 7 6 per cent.

From May, 1923, to January 1, 1957, there have been 1450 deaths among diabetic patients under our care at the New England Deaconess Hospital, 74 of these patients, or 5 1 per cent, entered in diabetic coma In Table 70 the fatal cases are listed by years. The causes of death in these cases are discussed in the following section

Causes of Death During Coma and After Discharge from the Hospital.—As stated above, there have been 74 deaths in the entire series of 969 attacks of coma in 704 patients A total of 177 patients who had coma prior

[59] Bertram Loc cit, p 350
[60] Best and Taylor P 574, Loc cit, p 165
[61] Falta P 101 Loc cit, p 79
[62] Joslin Jour Med Res, *6*, 306, 1901
[63] Tullis Am Jour Med Sci, *215*, 424, 1948

to 1940 were alive January 1, 1958 with an average duration of 21.3 years of diabetes!!

In Table 69 are listed the causes of death of 216 patients who died at various intervals after leaving the hospital following recovery from coma. Of 645 patients discharged, 641 have been followed up as of January 1, 1958.

TABLE 69.—CAUSES OF DEATH IN 216 PATIENTS AFTER RECOVERY FROM COMA, 1923–Jan. 1, 1958

	1923–1945	1946–1953	1954–1958
Nephropathy	0	41	28
Coma	12	10	6
Cardiac (Coronary sclerosis)	13	24	18
Tuberculosis	15	7	1
Miscellaneous	27	29	13
Total	67	113	66

The average duration of diabetes to date of death increased from 14.1 years for 180 patients prior to 1953 to an average of 21 years for patients dying between 1954 and 1958.

TABLE 70.—DEATHS IN COMA CASES COMPARED WITH TOTAL DIABETIC DEATHS

New England Deaconess Hospital, May 1923 to Jan. 1, 1957
(Authors' patients only)

	Total Diabetic Deaths	*Deaths in Coma Cases*	
		No.	*Per Cent of Total*
1923–1932	218	30	12.5
1933–1942	361	28	7.7
1943–1957	194	4	2.1
1948	61	2	3.2
1949	49	2	4.0
1950	70	0	0
1951	68	1	1.5
1952	72	2	2.8
1953	85	0	0
1954	63	3	4.8
1955	87	1	1.1
1956	92	1	1.1
	1450	74	5.1

The causes of death are listed under three periods of time according to the date of death. The striking changes in the incidence of nephropathy, coma and tuberculosis may be related to the fact that the average duration of diabetes to death has increased from 14.1 years for 180 patients in the first two periods to an average of 21 years for patients who died between 1954 and 1958. Nephropathy with terminal uremia now accounts for more than 42 per cent of the deaths, whereas tuberculosis, formerly a cause of 12.2 per cent of deaths, was present in only one of the last 66 cases. Under "Miscellaneous" are included: suicide, 1; status epilepticus, 1; cerebrovascular accidents, 6, and infections, 5.

Autopsy Findings.—Of our 74 fatal (hospital) cases, permission for a post-mortem examination was secured in 53 instances. In Table 71 are listed the chief causes of death in these cases

Study of Table 72 shows that 29 of the 53 patients had infections of serious degree, in most instances in themselves carrying a fatal prognosis However, there were 14 patients—more than one-fourth of the total—in whom autopsy disclosed no complication. These were needless deaths, the deaths due to neglect on someone's part.

TABLE 71.—CAUSES OF DEATH IN 74 CASES DURING OR FOLLOWING COMA

(January 1, 1923—January 1, 1957)

Causes of Death	*No*
Uncomplicated coma	21
Sepsis and metastatic infection	19
Pneumonia	12
Pancreatitis	3
Cardiac	3
Pulmonary embolism	1
Pulmonary infarct with empyema	1
Hemorrhage from duodenal ulcer	2
Cerebral hemorrhage	2
Alkalosis	1
Infected burn	1
Nephropathy (with anuria)	3
Acute edema of lungs	1
Encephalopathy	1
Total	74

TABLE 72.—DIABETIC COMA CAUSES OF DEATH IN 53 AUTOPSIED CASES DYING BEFORE HOSPITAL DISCHARGE (ONE HOUR TO SIXTY-THREE DAYS AFTER ADMISSION)

	Cases
[illegible]	14
[illegible]	15
[illegible]	2
Acute pancreatitis	3
Pneumonia	9
Other causes (1 case each with pulmonary embolism, infarct of lung with empyema, hemorrhage from duodenal ulcer, cerebral softening, and unexplained —? alkalosis, nephropathy, encephalopathy, and 3 from coronary occlusion)	10
	53

The serious character of [illegible] betic coma is well brought o [illegible] cemia and in two others in [illegible] (Cases 3267, 9987, and 10115) were found on post-mortem examination to have acute pancreatitis, these and a fourth case (14370) seen in another hospital were reported by Root[64] In this series of 4 cases the diagnosis of

[64] Root Jour Am Med Assn, *108*, 777, 1937

acute pancreatitis was not made during life; this experience illustrates strikingly the value of autopsies in patients dying in diabetic coma. Of the 7 cases reported by Tully and Lowenthal,[a] 4 died with acute pancreatitis Two of the four also had widespread chronic pancreatitic inflammation

I. WATER AND ELECTROLYTE METABOLISM IN DIABETIC ACIDOSIS

By Nancy Nichols, M.D.

Maintenance of Normal Body Fluid Composition.—In the healthy individual, a number of regulatory mechanisms are in constant interplay to preserve normal body hydration and to maintain electrolytes at physiological concentrations in the body fluids Table 73 presents the distribution of water and electrolytes in a normal 70 Kg. man, both in terms of total amounts, and in terms of that per cent of the total present in extracellular and [illegible]

tive [illegible]

that [illegible]

equality between these two compartments The mechanisms which operate to maintain these normal volumes and distributions of water and electrolytes include nutritive, hormonal, physicochemical, and renal factors. A surplus of water, to compensate for respiratory and skin losses and to provide an adequate urine volume for the excretion of excess electrolytes and metabolic end-products is normally ingested and absorbed daily. Sodium and chloride, the principal ions of the extracellular fluid, and potassium, magnesium and phosphate, the principal ions of the intracellular fluid, are all present in excess in the normal diet Under the influence of the glands of internal secretion, this water and these ions are selectively retained in quantities which will just preserve the proper volumes of intra- and extracellular fluid, and the normal concentrations of electrolytes in these fluids The intact cell membrane, at the normal pH of body fluids, acts as a selective barrier, maintaining high concentrations of phosphate, potassium, and magnesium within the cells in the face of low concentrations of these ions [illegible]

varying the rate of secretion and absorption of the individual electrolytes, and by the manufacture and substitution of ammonia and hydrogen ions for sodium and potassium, the kidney can conserve ions as well as dispose of them

Initial Metabolic Defects in Diabetic Acidosis.—During the development of diabetic acidosis, abnormalities occur in all of these homeostatic systems, and despite the development of a number of compensatory mechanisms by the body, usually result in marked dehydration, loss of electrolytes, and, eventually, metabolic acidosis The first step in the initiation of these abnormalities is the cessation of normal glucose metabolism due to

[a] Tully and Lowenthal Ann Int Med, *48*, 310, 1958

TABLE 73.—WATER AND ELECTROLYTE DISTRIBUTION IN A 70 KG MAN*

	H_2O		Na		K		Ca		Mg		Cl		PO_4=	
	Kg	*Per cent Total*	*mEq*	*Per cent Total*	*mEq*	*Per cent Total*	*mEq*	*Per cent Total*	*mEq*	*Per cent Total*	*mEq*	*Per cent Total*	*mEq*	*Per cent Total*
ECW[1]	Interstitial 10.5	21	2,100	60	56	1	70	< 1	42	2	1,680	100	28	< 1
	Plasma 3.5	7												
ICW[2]	35.0	72	385	11	5,600	99	70?	< 1	944	39	—	—	3,540	6
BONE	—		1,000	29	—	—	124,500	99	1,409	59	—	—	52,100	94
TOTAL	49.0	100	3,485	100	5,656	100	124,610	100	2,395	100	1,680	100	55,668	100

[1] Extracellular Water [2] Intracellular Water
* Compiled from the literature—Gamble[66], Bischoff[67], Edelman *et al*[68], Davies *et al*[69], Scholle[70], Mudge and Vislocky[71] and Nichols[72]

[66] Gamble Extracellular Fluid, Cambridge, Harvard University Press, 1942
[67] Bischoff Ztschr f rat Med, *20*, 75, 1863
[68] Edelman, James Baden, and Moore Jour Clin Invest, *33*, 122, 1954
[69] Davies, Kornberg, and Wilson Biochem Jour, *52*, XV, 1952
[70] Scholle Mineral Metabolism, New York, Reinhold Publishing Co, 1939
[71] Mudge, and Vislocky Jour Clin Invest, *31*, 850, 1952
[72] Nichols Proc Soc Exp Biol and Med, *97*, 363, 1958

a relative or absolute lack of insulin. This results in a number of changes in body metabolism First, blood sugar rises, producing hyperosmolarity of the extracellular fluid. A blood sugar of 500 mgm. per cent produces a *rise of about 17 milliosmols per liter of extracellular fluid.* In accordance with the laws of osmotic equilibrium, water will leave the intracellular fluid

FIG 21 Electrolytes of extracellular and intracellular fluid.

compartment, increasing extracellular fluid volume. A second effect of the cessation of carbohydrate metabolism is the appearance of ketone bodies in the plasma[73] which also increases plasma osmolarity Normally, fat is metabolized to carbon dioxide and water in the tricarboxylic acid cycle. However, in order to enter this cycle, the two-carbon fragment acetyl CoA or "active acetate," derived from fat, must combine with a molecule of

[73] Petters, Vierteljahrschr f die praktische Heilkunde, *55*, 81, 1857

oxalacetate, which is derived from carbohydrate or portein [74,75] In diabetic acidosis fat is metabolized, but because of the lack of oxidation of carbohydrate, and the inability of protein catabolism to supply sufficient oxalacetate, there is a relative lack of this substance, and the acetate fragments derived from the utilization of fat accumulate in the liver cells and condense to form acetoacetic acid which then appears in the plasma in the form of acetoacetic and beta-hydroxybutryic acids and acetone [76] These ketone [illegible]

in plasma volume resulting from the combination of extracellular hyperosmolarity and protoplasmic catabolism leads to an increased cardiac output, which in turn leads to an increased rate of glomerular filtration, resulting in less reabsorption of water than usual by the proximal tubules of the kidney, and produces the osmotic diuresis or polyuria seen early in the development of diabetic acidosis

The ketone acids, in addition to increasing extracellular osmolarity, increase the anionic constituents of the blood plasma and unless neutralized or excreted cause a rapid fall in plasma pH[78 79] Excretion of these acids, as well as increased excretion of potassium, magnesium, and phosphate, the main intracellular electrolytes, is noted early in diabetic acidosis [80 81 82]

Homeostatic Defense Mechanisms.—In this initial stage of the development of ketoacidosis, the body mobilizes a number of defense mechanisms in an attempt to preserve homeostasis These mechanisms are fourfold: the action of the body buffers, hormonal responses, renal defense mechanisms, and mobilization of body base stores

The body has a number of buffer systems in the intra- and extracellular fluids, and in the cell solids, which can operate to compensate for changes in the constitution of the normal electrolyte pattern The most important of these buffers is extracellular bicarbonate In the normal individual, with physiological concentrations of electrolytes in the body fluids, and a resulting extracellular pH of between 7 38 and 7 42, the ratio of carbonic acid ($H\,HCO_3$) to bicarbonate ($B\,HCO_3$) is 1 20 [83] When ketone acids are added to the plasma, $B\,HCO_3$ is reduced, as B (mainly sodium, in plasma) is used to neutralize these acids This leads to an increase in $H.HCO_3$, and

[74] [illegible]

60, 102, 1947

[82] Guest Loc cit p 370

[83] Van Slyke and Cullen Jour Biol Chem, *30*, 289, 1917

an increased ratio of carbonic acid to bicarbonate, resulting in a fall in plasma pH. The increased amount of carbonic acid in the plasma (or the increased pressure of carbon dioxide (pCO_2) resulting from the increased carbonic acid) stimulates the respiratory center to increase its depth and frequency of respiration [84] Since the concentration of carbonic acid in the blood is directly dependent on the concentration of carbon dioxide in the alveolar air of the lungs, increasing th

and rate of respiration will enable the lungs to further lower the concentration of carbon dioxide in the residual air. Although none of these respiratory changes can raise $B.HCO_3$ in the plasma, they can and do diminish $H.HCO_3$ Since it is the ratio of $H.HCO_3$ to $B.HCO_3$ that determines pH, rather than the absolute amounts of either substance, reduction of carbonic acid will tend to restore this ratio towards normal and preserve normal pH Clinically, hyperpnoea or "Kussmaul"[85] breathing is observed, and measurement of total blood CO_2 will show a lower than normal value

Other body buffers also respond to the abnormal accumulation of ketone acids,[86, 87] lactic acid[88, 89] and other organic acids in the plasma [90] All of the body proteins have a diminished basebinding capacity at lowered pHs [91] Therefore, as ketones reach th
bumin and globulin decreases
the ketones, and neutralize ther
intracellular proteins are much more important quantitatively. In the red cells, hemoglobin lowers its anion equivalence[92] freeing intracellular potassium and magnesium to combine with the organic acids that accumulate in the cells as a result of abnormal metabolism [93] In the muscle cells, myoglobin behaves in the same way. Phosphate, the main intracellular anion of all cells, also acts as a buffer under these conditions [94] At a normal intracellular pH of about 6 95[95, 96] (intracellular pH is somewhat lower than extracellular pH, due to a higher concentration of hydrogen ions within cells than in plasma) phosphate has a valence of 1 8 This results from the fact that at this pH some 20 per cent of intracellular phosphate ions combine with one base equivalent, while 80 per cent combine with two base equivalents [97] At an intracellular pH of 6 70 (resulting from an extracellular pH of 7 2), the dissociation constant of phosphate is only 1 4 This is due, in large part, to the diminution of organic ester phosphates, normally present

[84] Gray Science, *103*, 739, 1946
[85] Kussmaul Deutsch Archiv f klin Med, *14*, 1, 1874
[86] Hardy Proc Roy Soc, *66*, 110, 1900
[87] Loeb Proteins and the Theory of Colloidal Behaviour, New York, McGraw-Hill, 1924
[88] Hartmann Arch Int Med, *56*, 413, 1935
[89] Meier and Thoenes Arch f exp Path and Pharmac, *161*, 119, 1931
[90] Kirk Ugesk f Laeger *104*, 566, 1942
[91] Theorell Biochem Ztschr, *252*, 1, 1932
[92] Loeb Loc cit p 382
[93] Hartmann Loc cit p 382
65, 2355, 1943
Jour Biol Chem, *54*, 481, 1922

as carbohydrate intermediates, leading to an accumulation of inorganic phosphate, which is a weaker acid than these esters[98] This represents the release of one equivalent of base for every four and one half equivalents of phosphate,[99] and allows a certain accumulation of acids, and loss of base to occur in the cells without change in pH.

A second defense mechanism of the body lies in its hormonal responses The individual developing diabetic coma is in a state of stress, which affects the hypothalamic-pituitary-adrenal axis In so far as carbohydrate metabolism is concerned, almost all of the responses to stress are adverse, tending to increase blood sugar levels and inhibit carbohydrate metabolism[100,101] But in the case of electrolyte metabolism, at least one useful mechanism comes into play. The increased output of epinephrine under stress causes an increased secretion of adrenocorticotropic hormone;[102] this, in turn, leads to the elaboration of increased amounts of adrenal cortical hormones, including those of the 11-desoxy group, concerned with electrolyte metabolism[103] These hormones, of which aldosterone is the present prototype[104,105] act directly on the renal tubules, stimulating them to retain sodium and excrete potassium[106] Since the extracellular fluid is, at this time, receiving large amounts of potassium from the cells, as glycogen and ... ...ct, promoting

...ne during the ... In the early stages of coma, although there is a marked diuresis, the volume of the extracellular fluid is well maintained, due to polydipsia and the withdrawal of water from the cells in response to plasma hyperosmolarity No increased secretion of antidiuretic hormone would therefore be expected to occur in the primary phases of acidosis[107 108 109] Later in coma, as water intake ceases, extracellular fluid volume decreases but urinary water loss continues unchecked The failure of antidiuretic hormone to check this dehydration may be due to several causes Despite a total hyperosmolarity of plasma, there may be a specific low level of plasma sodium or chloride and the hypothalmic osmoreceptors may not respond to increased levels of more diffusible ions such as glucose, ketone bodies, and other organic acids[110] Another possible explanation would be that the excretion of these later substances takes precedence, at a tubular level, over the conservation of water In

[98] Kumler and Eiler Loc cit, p 382
[99] Clark Topics in Physical Chemistry, Baltimore, Williams and Wilkins, p 278 1952
[100] Selye Jour Clin Endocrinol, *6*, 117, 1946
[101] Himsworth Lancet, *1*, 465, 1949
[102] Selye Loc cit p 383
[103] Tait, Simpson, and Grundy Lancet, *1*, 122, 1952
[104] Deming and Luetscher Proc Soc Exp Biol and Med, *73*, 171, 1950
[105] Simpson, Tait, Wettstein, Neher, Von Euw and Reichstein Experientia, *9*, 333, 1953
[106] Spiers, Simpson and Tait Endocrinology, *55*, 233, 1954
[107] Gilman and Goodman Jour Physiol, *90*, 113, 1937
[108] Verney Lancet, *2*, 759, 781, 1946
[109–110] Verney Proc Roy Soc, London, *135*, 27, 1947

any event, conservation of water by secretion of concentrated urine does not occur during the development of ketoacidosis.[111, 112, 113]

The kidney activates a number of mechanisms early in the course of diabetic ketosis designed to preserve normal electrolyte concentrations in the body. The osmotic diuresis which results from plasma volume expansion enables it to excrete large amounts of ketone acids, organic acids, potassium, and phosphate.[114] Except for potassium, the electrolyte load presented for excretion consists almost entirely of anions.[115, 116] Aided by an increased output of adrenal cortical hormones, the kidney can utilize all of the potassium presented to it to neutralize these anions.[117] Three other mechanisms are stimulated to aid the kidney to excrete its acid load while conserving fixed body base. The first of these is the excretion of free organic acids in the urine by the elaboration and substitution of hydrogen for sodium, potassium, and magnesium. Although ketones and other organic acids are 100 per cent combined with base in plasma, they may be excreted in large part in a free state in acid urine, thereby conserving body base.[118, 119] The second mechanism for base conservation is the conversion of dibasic phosphate to monobasic phosphate, with subsequent retention of sodium. The ratio of dibasic (Na_2HPO_4) to monobasic (NaH_2PO_4) phosphate in plasma is 4:1, in urine with a pH of 6.0 this ratio is not only reversed but actually 9 molecules of monobasic phosphate are excreted for one molecule of dibasic phosphate.[120] At a pH of 4.8 (the limit of acidity for urine,[121]) 99 to 100 per cent of phosphate is excreted as the monobasic salt,[122] representing a major conservation of body base. The third way in which fixed base is conserved by the kidney is by the secretion of ammonia by the tubular cells,[123] and its substitution there for the plasma cations which would otherwise be excreted in combination with anions. Increased production of ammonia in response to acidosis occurs almost immediately, although maximal ammonia production is not reached for several days.[124, 125] Whereas the normal individual excretes some 30–50 mEq. of ammonia in a day, the diabetic in acidosis may excrete more than 500 mEq.[126] A final compensatory mechanism which the kidney could activate in the conservation of normal body composition would be the excretion of a concentrated urine. However, limitation of urine concentration is a constant finding

[111] Butler, Talbot, Burnett, Stanbury, and MacLachlan. Loc. cit., p. 381.
[112] B[illegible] Arch. Int. Med., 36, 859, 1925.
[illegible], 1914.
[illegible] Yale University Press, p. [illegible]
[123] Nash and Benedict. Jour. Biol. Chem., *69*, 381, 1926; *82*, 673, 1929.
[124] Ryberg. Acta Physiol. Scandinavia, *14*, 114, 1948.
[125] Sartorius, Roemmelt, and Pitts. Jour. Clin. Invest., *28*, 423, 1949.
[126] Smith. The Kidney, New York, Oxford University Press, p. 400, 1951.

early in diabetic ketosis,[127 128 129] possibly due to the inhibition of production of antidiuretic hormone already discussed.

Despite substitution and conservation by the kidney, some sodium is nevertheless lost from the extracellular fluid in the early stages of acidosis [130,131,132,133] Replacement of this sodium can occur by direct addition to the extracellular fluid from bone crystals, under the stimulus of a lowered plasma pH, or a fall in the concentration of serum sodium.[134 135] Some 30 per cent of the total body sodium is present in bone,[136] and about 10 to 15 per cent of this sodium, representing 100-200 mEq in an adult, can be released by the substitution of calcium or hydronium ions at the surface of the bone crystals [137 138]

If the interplay of all of these physico-chemical defense mechanisms is successful, extracellular fluid volume and extracellular and intracellular electrolyte composition are maintained at near normal levels, although [illegible]

still in this compensated state, and he passes into the phase of uncompensated acidosis.

Uncompensated Ketoacidosis.—Uncompensated acidosis is characterized by very low levels, usually less than 9 mEq, per liter, of plasma carbon dioxide, accompanied by a fall in plasma pH Total serum carbon dioxide levels as low as 1 3 mM have been reported,[139] and pHs as low as 6 8 have been recorded in this clinic in patients with fully developed severe acidosis [140] Associated with this, one finds varying degrees of dehydration and, depending on the factors initiating and complicating the acidosis, and its duration, various abnormal changes in electrolytes [141 142 143,144,145] Finally shock, renal failure and alterations in cellular metabolism, due to the inhibitory effect of low pH on intracellular metabolism or the effect of specific ion abnormalities, manifest themselves

A quantitative estimation of the severity of the acidosis from the meas-

[illegible] 381

230, 1952

, 1952
381
Loc cit p 381

urement of total plasma carbon dioxide at this time is not possible.[146, 147, 148, 149, 150] It is apparent that any patient with a carbon dioxide combining power of less than 9 milliequivalents per liter has, or will have shortly, an uncompensated acidosis. *However, when patients are seen with CO_2 values of four or five milliequivalents per liter, as is frequently the case, these values are of little use in accurately evaluating the severity of the existing acidosis.* Values such as these represent exhaustion of the buffering capacity of plasma CO_2, and may have just been reached or may have been present for many hours. The degree of uncompensated acidosis actually existing will depend on the severity of the biochemical stresses to which the patient has been subjected and the length of time that these stresses have been going on. The most useful criteria of the degree of acidosis is the plasma pH, for this is the end result of all of the forces operating to preserve normal body composition versus all of those mechanisms which are responsible for the acidosis. As acidosis progresses unchecked, plasma pH will fall progressively until the lowest limits compatible with life, about 6.8,[151] are *reached. Since intracellular pH is lower than extracellular pH,*[152, 153] *acidity* greater than this cannot be tolerated, as cell metabolism ceases.

In the patient who does not receive, or respond to, insulin, the complications of uncompensated acidosis progress steadily and inexorably. This is due to the persisting high blood sugar, with its concommitant production of intracellular dehydration, the continuing production of ketone bodies by the liver and organic acids by the cells, the exhaustion of body buffer capacity, dehydration, extracellular fluid loss, shock, and renal failure. The rate of occurrence of these conditions depends on a number of factors: the initial state of nutrition and dehydration of the patient, the presence or absence of organic renal disease, the fluid intake during the early hours of illness, and complicating factors such as fever, vomiting, or diarrhea.

It is important for the physician to realize that the patient developing diabetic ketoacidosis has, except for food in the gastrointestinal tract and urine in the bladder at the time of onset, virtually no excess electrolytes or water in his body. Once food and fluid intake have ceased, all losses represent destruction of the normal body mass. Although food intake and carbohydrate utilization cease early in the course of acidosis, polydipsia is present at this time, and prevents the rapid progress of dehydration that is seen as the patient enters the later or uncompensated phase of acidosis. In this later phase, nausea, vomiting, and malaise cause a cessation of water intake, *and all of the water that is lost in the urine is now derived from the* extra- and intracellular fluids. This fluid, furthermore, is not available as "free" water, with which to excrete excess acids and electrolytes. Both intra- and extracellular water have an osmolarity of about 305 millosmols per liter (Figure 21). When the extra- and intracellular fluids are lost

[146] Atchley, Loeb, Richards, Benedict and Driscoll. Loc. cit., p. 381.
[147] Rabinowitch, Fowler and Bensley. Ann. Int. Med., *12*, 1403, 1939.
[148] Almy, Swift, and Tolstoi. Jour. Am. Med. Assn., *129*, 863, 1945.
[149] Sprague. Med. Clin. North Am., *31*, 415, 1947.
[150] Guest. Loc. cit., p. 370.
[151] Van Slyke. Jour. Biol. Chem., *48*, 153, 1921.
[152] Wallace and Hastings. Loc. cit., p. 382.
[153] Fenn and Maurer. Protoplasma, *25*, 22, 1935.

through the kidney, these ions must also be excreted. Furthermore, the usual concentration of sugar in the urine of these patients is between 3 and 4 per cent,[154] representing about 30 to 40 grams of glucose, or 166 to 222 millimols per liter. At a maximal urinary concentration of 1.4 osmolar,[155] this would enable the kidney to excrete another 1200 millimols of solutes per liter. However, maximal urine concentration does not occur in diabetic acidosis[156,157] and usually only 200 to 300 "excess" ions can be excreted with each liter of body fluid that is lost Not only is fluid lost by the kidney, but also through the skin and lungs The normal, afebrile individual has an insensible water loss from these two sources of approximately 11.5 to

TABLE 74 —LOSSES OF WATER AND ELECTROLYTE DURING DIABETIC COMA, IN A 70 KG (154 LB) MAN *

	ECW[1]		*ICW*[2]		*Total*	
	Gms	*Per Cent Total*	*Gms*	*Per Cent Total*	*Gms*	*Per Cent Total*
H_2O	3810	27	3830	11	6866	14
	mEq		*mEq*		*mEq*	
Na	591	28	26	7	351	15
K	7 8	14	490	9	493	9
Ca	—	—	—	—	252	002
Mg	—	—	58	6	56	2
Cl^-	420	25	—	—	430	26
$PO_4^{\equiv}$	—	—	—	—	344	006

[1] Extracellular Water [2] Intracellular Water

*Average values, compiled from the data of Atchley *et al*,[158] Butler,[159,160] and Nabarro[161]

12 cc /Kg/day, or 800–850 cc in a 70 Kg man[162,163] In a febrile, hyper-

electrolytes Table 74 presents average values for losses of water and electrolytes in patients with severe ketoacidosis There is an average loss of about 7 liters of total body water About half of this is derived from the intracellular fluid, most of which represents losses early in the development of

[154] Average value for 153 cases studied at the New England Deaconess Hospital, 1946-1951

Loc cit, p 381
384

[164] Dubois Basal Metabolism in Health and Disease, Philadelphia, Lea and Febiger, 1946
[164] Gamble Loc cit, p 384
[164] Coon Arch Int Med, 83, 416, 1949

acidosis, while the remainder represents loss of extracellular fluid, sustained largely in the later stages when water intake has ceased. It is at this time that marked contraction of the size of the extracellular fluid space occurs, with hemoconcentration and a decrease in plasma volume,[166 167] and finally a decline in blood pressure. As the blood pressure falls, there is a decrease in the amount of blood reaching the kidneys, and renal ischemia results. Numerous granular casts appear in the urine in severe diabetic acidosis, due to lesions of the tubules described by Oliver as "tubulorhexis," where entire tubules, or portions of them may be destroyed.[168] Although the glomeruli do not appear to be structurally damaged,[169] they must have an altered permeability, for large quantities of albumen also appear in the urine. Interestingly, tubular ammonia production may remain unimpaired.[170] As ischemia progresses and the blood pressure continues to decline, there is a decrease in the rate of glomerular filtration[171 172] and the elaboration of urine is curtailed or ceases.

Table 74 shows that sodium and chloride are lost in proportions approximately representing their relative concentrations in the extracellular fluid. Some 25-30 per cent of the total extracellular fluid is excreted before renal ischemia causes oliguria. The fact that balance studies indicate a greater loss of sodium from the extracellular compartment than from the total body probably represents unmeasured losses of sodium in sweat or feces. Potassium loss is mainly from the intracellular space, as has been discussed. The ratio of potassium to nitrogen in intact protoplasm is 1:2.7; that is, for every gram of nitrogen there are present 2.7 mEq. of potassium.[173 174] Comparison of the relative excretion of nitrogen and potassium in these patients reveals that amounts of potassium considerably in excess of this ratio are lost during diabetic coma.[175 176] In the early stages, this probably represents glycogen destruction, while later, following marked loss of intracellular water, potassium is probably extruded from the cell in an effort to reduce hyperosmolarity of the remaining intracellular water. Losses of magnesium are less, and, again, are almost entirely intracellular. There is an average loss of some 344 mEq. of phosphate, but because of the very high concentration of phosphate in bone, this represents only a minute fraction of the total body stores of this ion. If one presumes, as seems logical, that most of this phosphate is lost from the intracellular water, it is equivalent to a loss of some 10 per cent of total intracellular phosphate.

Certain complications may cause even more marked loss of individual [illegible] [177]

[illegible] 1951
[illegible] 1951
[illegible] t., 30, 1305, 1951
[illegible] Press, p. 649, 1951
[illegible] 935
[illegible] 39
[illegible] Loc. cit., p. 381
[illegible] in., 5, 367, 1945

in severe hyponatremia, or further intracellular loss of potassium.[178,179,180] Conversely, if initial dehydration existed, or if oliguria was present, preventing diuresis in the early stages of acidosis, potassium retention and hyperkalemia may be present.[181,182]

As the uncompensated phase of ketoacidosis continues, catabolism of

are fully developed, and in addition, acute renal failure is present. Without therapy the patient can survive only a short time

The clinical picture of the patient with severe, uncompensated diabetic acidosis reveals the major chemical abnormalities that exist within him He is prostrate, possibly comatose. Usually he is breathing deeply and

nsion of the thorax, ex-
scribed by Kussmaul[183]
Kussmaul breathing in
diabetic ketoacidosis is indicative of extreme prostration with failure of the respiratory center to respond to the decreased plasma carbon dioxide. The high level of blood ketones may be readily apparent through a sweet, 'fruity' odor of the breath. Dehydration is evident in the dry skin and mucous membranes, and soft eyeballs, as well as in the oliguria or anuria which is present The decreased plasma volume secondary to dehydration leads to a fall in blood pressure, and cold, cyanotic extremities If hyperpotassemia is present there may be weakness or flaccid paralysis of the

sodium may be normal or low [192,193,194,195,196,197] If the patient has had a

, 1949

Sci, *218*, 308, 1949

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t, p 381

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35

385

t, p 381

Loc cit, p 381

...abatto, Spencer, and Stowers Loc cit, p 385

196 Nichols and Nichols Loc cit, p 385

197 Sprague Loc cit p 380

great deal of vomiting, hypochloremia may have developed.[198,199] Serum phosphate may be normal or high.[200,201] And, although they are not usually measured clinically, a high level of abnormal organic acids, besides ketone acids, up to 195 mgm. per cent may be present in the plasma.[202,203,204,206] It [illegible]

Principals of Replacement Therapy.—*The fluid therapy of diabetic ketoacidosis falls into three phases. In the first hours of treatment the prompt administration of adequate amounts of fluid and electrolytes is of paramount importance to restore the blood pressure to normal levels and to replace the intra- and extracellular fluids and electrolytes that have been lost. In addition, sufficient water must be given to reinstate a good urine flow and permit the excretion of accumulated catabolites, and to compensate for continued insensible water loss. It is impossible to determine the exact amount of fluid that has been lost in any individual case.* However, there is some agreement between measurements made by various workers, by the techniques of estimating losses, measuring actual losses, and measuring water retention during the first 48 hours of treatment. Soskin and Levine, assuming that weight loss represented water loss, estimated an average loss of seven liters of fluid in a 70 Kg adult.[207] Butler found a loss of 6.3 liters in an individual fasted and thirsted for 4 days.[208] Nabarro and his co-workers, studying water retention in 7 patients recovering from diabetic acidosis, found water retentions varying from 5.1 to 6.5 liters per 70 Kg. of body weight, with an average retention of 6.0 liters, excluding one patient who, though weighing only 21 Kg., retained 11.2 liters.[209] It appears from these data that the average loss of water in a 70 Kg. individual with severe diabetic ketosis varies from about 6 to 7 liters, as shown in Table 74. *Much greater quantities of fluid than this are occasionally needed to restore water balance in diabetic patients,* as was seen in one of Nabarro's patients, and as has been reported by Root and Riseman, who gave 13,800 and 11,600 cc. of fluid to two patients during the first 29 hours of treatment.[210] Replacement fluids should, of course, be given with caution, in order that the cardio-vascular system may not be overloaded, resulting in pulmonary edema. In practice, however, this is rarely seen if the patient is followed carefully and parenteral rehydration stopped when an adequate urine flow has been established.

198 Gamble and Ross. Loc. cit., p. 388.
199 Gamble and MacIver. Jour. Exper. Med., *48*, 837, 1928.
200 Guest. Loc. cit., p. 381.
201 Seldin and Tarail. Loc. cit., p. 385.
202 *Butler et al.* Loc. cit., p. 381.
203 Bertram. Die Zuckerkrankheit, Leipzig, George Thieme, 2d Ed., p. 51, 1939.
204 Poulsen. Studies on the Ketosis in Diabetes Mellitus, Steno Memorial Hospital, Copenhagen, 1941.
205 Root. Jour. Am. Med. Assn., *127*, 557, 1945.
206 Nichols and Nichols. Loc. cit., p. 385.
207 Soskin and Levine. Am. Jour. Digest. Dis., *11*, 305, 1944.
208 Butler. Loc. cit., p. 387.
209 Nabarro *et al.* Loc. cit., p. 385.
210 Root and Riseman. Jour. Am. Med. Assn., *110*, 1730, 1938.

The most commonly used replacement fluid in the initial treatment of diabetic acidosis is so-called "physiological" or 0.85 per cent salt solution. Actually, this solution is not physiological, since it contains about 145 millimols of both sodium and chloride, while the extracellular fluid contains about 145 millimols of sodium, but only about 110 millimols of chloride. This excess chloride is deleterious in three ways, it unnecessarily increases the hyperosmolarity of the already dehydrated plasma, it increases the existing acidosis in the plasma, and it puts an extra excretory load on the kidneys, both in terms of total milliosmols and in terms of base equivalents. A replacement solution in which some 35 millimols of chloride are replaced by lactate or bicarbonate is, therefore, preferable, and such solutions, containing a balanced mixture of sodium chloride and sodium lactate or bicarbonate, are readily available today. A further refinement of therapy which has been introduced is the use of hypotonic solutions. The rationale for the use of such fluids is based on the fact that during the development of ketosis, there is a loss of water in excess of fixed electrolyte due to the

Butler advocates the use of a hypotonic salt solution, to which enough sodium bicarbonate or lactate has been added to create a sodium:chloride ratio of 1.3 to 1.[311] The total osmolarity of such a solution should not be

that hypotonic solutions are superior to isotonic ones, they should only be used by those thoroughly familiar with such therapy, and in a hospital. For most purposes, a commercial isotonic sodium chloride sodium lactate or bicarbonate solution will prove most satisfactory, and if this is not available, 0.85 per cent saline should be used without hesitation. The use of intravenous fluids should be discontinued as soon as the patient is conscious, has ceased vomiting, and is able to take and retain fluids by mouth. This will usually occur after the administration of two to four liters of fluid, although in some cases much more than this may have to be administered intravenously.

The second phase of treatment is directed towards sustaining normal extracellular fluid volume and composition, maintaining adequate urine outflow, beginning to provide for the restoration of intracellular water and electrolytes, and correcting any specific ion defects that are found to be present. The most common of these is hypokalemia.

[311] Butler. Loc. cit., p. 387.
[312] Latta. Lancet, 2, 274, 1831–32.

Levels of plasma potassium are usually normal or elevated in patients admitted in diabetic coma.[213,214,215] Within a few hours after treatment is initiated, however, there is usually a precipitous fall in the plasma concentration of this ion.[216,217,218] At least three mechanisms are responsible for this fall; namely, dilution of extracellular potass[illegible]

[illegible] ... considered that large [illegible]

[illegible] ... in ion-replacement therapy by Gamble.[220] Furthermore, as far as is known at present, there is [illegible]

[illegible] plasma [illegible] ... can be rapidly determined by flame photometry. Levels below 3 mEq./Liter call for prompt but cautious administration of this salt, parenterally if the patient cannot take fluids orally. Fifty to one hundred mEq. of potassium may be safely given intravenously in a liter of saline over a period of two hours, to patients with adequate urine flow. If hypo-kalemia [illegible]

[illegible] ... one does not wish to add chloride ion, for reasons already discussed, potassium acetate or potassium lactate may be added in appropriate quantities. Although a low plasma potassium indicates a lack of this ion, the exact relationship of plasma levels to intracellular concentrations is not known, and restoration of plasma levels to norm[illegible]

[illegible] ... maintain extracellular fluid volume and allow for the excretion of remaining abnormal anions. If the patient cannot take fluids by mouth, isotonic sodium chloride may now be given. Orally, broth, milk, and orange juice provide sodium and potassium, as well as fluid. Depending on the blood sugar levels, glucose administration, again either orally, or intravenously as 5 per cent solution, may be necessary.

213 Seldin and Tarail. Loc. cit., p. 385.
214 Nabarro and others. Loc. cit., p. 385.
215 Nichols and Nichols. Loc. cit., p. 385.
216 Butler. Loc. cit., p. 385.
217 Holler. Jour. Am. Med. Assn., *131*, 1186, 1946.
218 Frenkel, Groen, and Willebrands. Arch. Int. Med., *80*, 721, 1947.
219 Von Bunge. Ztschr. Physiol. Chem., *28*, 452, 1899.
220 Gamble. Loc. cit., p. 379.
221 Danowski, Peters, Rathbun, Quashnock and Greenman. Jour. Clin. Invest., *28*, 1949.
222 Tarail and Elkinton. Ibid., 99, 1949.
223 Narbarro, *et al.* Loc. cit., p. 385.
224 Nichols and Nichols. Loc. cit., p. 385.

tion of large quantities of this ion, in the period of recovery from diabetic coma, reflects the need for replacement of intracellular deficits of potas-

diet should contain adequate amounts of foods rich in this ion (such as meat, broths and cereals) to permit the deposition of glycogen and protein and to repair the potassium losses in excess of nitrogen that have occurred. The only contraindication to the administration of potassium in diabetic ketosis is renal impairment, with anuria or marked oliguria. As the life-span of the diabetic increases, more patients with severe renal disease will be seen, and the problems of potassium administration in coma will increase.

Just as potassium is the main intracellular cation, phosphate is the main intracellular anion, and, in many respects its behaviour parallels that of potassium. Hyperphosphatemia on admission, followed by hypophosphatemia during treatment, has been reported by several investigators[233, 234] and has led to the suggestion that potassium phosphate be used in the treatment of diabetic acidosis.[235, 236] Although there is unequivocal evidence that phosphate is concerned with carbohydrate metabolism, we have at present no clear-cut evidence that the administration of phosphate salts materially improves the utilization of carbohydrate in ketotic patients. This may be related to the fact that the absolute loss of phosphate during the development of coma is less than the loss of potassium, and closely parallels the loss of r

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of c

C

present time, but theoretical considerations show that there may be a rationale for its use

be high and serum cal

calcium is increased.[240]

[225] Seldin and Tarail Loc cit, p 385
[226] Nabarro and others Loc cit, p 385
[227] Nichols and Nichols Loc cit, p 385
[228] Butler Loc cit, p 385
[229] Danowski, *et al* Loc cit, p 392
[230] Seldin and Tarail Loc cit, p 385
[231] Nabarro, *et al* Loc cit, p 385
[232] Butler Loc cit, p 378
[233] Butler Loc cit, p 378
[234] Franks, Berris, Kaplan and Myers Arch Int Med, *81*, 42, 1948
[235] Guest Loc cit, p 381
[236] Franks, *et al* Loc cit, p 393
[237] Weinhouse, *et al* Loc cit, p 381
[238] Atchley, *et al* Loc cit, p 381
[239] Nabarro, *et al* Loc cit, p 385
[240] Dillman and Visscher Jour Biol Chem, *103*, 792, 1933

Levels of plasma potassium are usually normal or elevated in patients admitted in diabetic coma.[212, 213, 214] Within a few hours after treatment is initiated, however, there is usually a precipitous fall in the plasma concentration of this ion.[216, 217, 218] At least three mechanisms are responsible for this fall; namely, dilution of extracellular potas...

... sium caused ... large loads ... a marked increase in the urinary excretion of potassium. This has been confirmed in fluid-replacement therapy by Gamble.[219] Furthermore, as far as is known at present, there is no completely adequate hormonal or enzymatic mechanism for the renal conservation of potassium. Continued excretion of potassium is observed even in patients with markedly diminished body contents of this ion.[221, 222] The level of plasma potassium can be rapidly determined by flame photometry. Levels below 3 mEq./Liter call for prompt but cautious administration of this salt, parenterally if the patient cannot take fluids orally. Fifty to one hundred mEq. of potassium may be safely given intravenously in a liter of saline over a period of two hours, to patients with adequate urine flow. If hypokalemia persists, as evidenced by low plasma potassium levels, this can be repeated. If the patient is able to take fluid orally, 50 mEq. of KCl may be added to a glass of orange juice. If one does not wish to add chloride ion, for reasons already discussed, potassium acetate or potassium lactate may be added in appropriate quantities. Although a low plasma potassium indicate...

... to maintain extracellular fluid volume and allow for the excretion of ... If the patient cannot take fluids by ... now be given. Orally, broth, milk, a ... potassium, as well as fluid. Depending on the blood sugar levels, glucose administration, again either orally, or intravenously as 5 per cent solution, may be necessary.

[212] Seldin and Tarail. Loc. cit., p. 385.
[213] Nabarro and others. Loc. cit., p. 385.
[214] Nichols and Nichols. Loc. cit., p. 385.
[215] Butler. Loc. cit., p. 385.
[216] Holler. Jour. Am. Med. Assn., *131*, 1186, 1946.
[217] Frenkel, Groen, and Willebrands. Arch. Int. Med., *80*, 721, 1947.
[218] Von Bunge. Ztschr. Physiol. Chem., *28*, 452, 1899.
[219] Gamble. Loc. cit., p. 379.
[220] Danowski, Peters, Rathbun, Quashnock and Greenman. Jour. Clin. Invest., *28*, 1, 1949.
[221] Tarail and Elkinton. Ibid., 99, 1949.
[222] Narbarro, *et al.* Loc. cit., p. 385.
[223] Nichols and Nichols. Loc. cit., p. 385.

Chapter 14

ALLERGY AND DIABETES

ALEXANDER MARBLE, M D

ALLERGIC conditions may exist in diabetic patients, just as in non-diabetics, and when present may complicate treatment In addition, a diabetic may exhibit hypersensitiveness to insulin, which may not only cause discomfort but also at times seriously hamper needed treatment

A HYPERSENSITIVENESS TO INSULIN

Shortly after the discovery of insulin, reports began to appear of allergic phenomena developing after its use One of the earliest papers[1] described 4 cases of urticaria which appeared among the first 83 patients treated with insulin There has been considerable discussion as to whether these reactions represent a true allergic response to insulin itself Some[2] have presented evidence that the untoward responses are due to impurities in insulin rather than to insulin itself However, in a practical way as viewed by the physician, the responses represent hypersensitiveness to insulin as commonly available on the market As might be anticipated, dermal reactions to insulin are not confined to diabetic individuals, Blotner[3] found an incidence of 31 per cent among 100 non-diabetic persons given insulin to promote weight gain

Types of Allergic Manifestations —The most common allergic reactions [illegible]

types Patients usually describe a stinging, burning, or itching sensation at the site of the injection, and in from one-half to several hours the affected tissues become indurated The indurations may vary from one to several centimeters in diameter, may be warm to touch, and may be surrounded by a small or large area of erythema Pain or soreness is present in almost all cases In some patients the indurations disappear in from six to twenty-four hours while in others each area may last several days

Far more spectacular, and fortunately much less common, are the generalized allergic reactions[4] Chief among these are the urticarial responses which are annoying mainly because of the associated itching Frequently

[1] Joslin, Gray, and Root Jour Metab Res, *2*, 651, 1922
[2] Jorpes Arch Int Med, *83*, 363, 1949 Idem Acta Med Scand (Supp 239), *138*, 313, 1950
[3] Blotner New England Jour Med, *218*, 371, 1938
[4] Stone, Frankel and Baker Jour Clin Invest, *9*, 895, 1949

calcium may be present before the onset of acidosis. As fluid therapy expands the extracellular space, total serum calcium levels will drop and, as pH rises, the amount of ionized calcium present will diminish, possibly resulting in tetany. In theory, therefore, the addition of small amounts of calcium to replacement fluid, is justified. The fact that this situation has not been recognized clinically tends to support the concept that it is the ratio of ionized calcium to potassium that determines muscle irritability, for serum potassium falls together with calcium in the treatment of ketoacidosis.

died in diabetic coma [13] Case 26598 developed anaphylactic shock following the first injection of insulin she ever received but fortunately recovered, was desensitized and later received insulin without difficulty. Wechsler *et al.*[14] describe a sixty-five year old woman who had three such reactions, the first of which simulated a coronary occlusion

TABLE 75 —CLASSIFICATION OF DERMAL REACTIONS
(After Paley and Tunbridge)

1 Mild Local Reactions
 A Immediate
 [illegible]
 B [illegible]
  Similar to the immediate reaction, but onset delayed 6 to 24 hours after injection
2 Severe Local Reactions
 A. Immediate
 [illegible]
  Identical with previous reaction, but onset delayed 6 to 24 hours after injection
3 Generalized Reactions
 Not encountered in series of Paley and Tunbridge
4 Pseudo-Reactions

Incidence.—The incidence of untoward skin responses to insulin, as noted by various observers, has varied from less than 10 per cent[15, 16] to 55 8 per cent [17] The differences are due chiefly to the degree of care with which patients are examined following injections of insulin and whether or not one includes mild responses The high incidence reported by Paley and Tunbridge[18] was found in the diabetic clinic of the General Infirmary at Leeds, England, and concerned 147 patients who started treatment in the years 1947–1949 They noted that a larger proportion of the females (65 per cent) than of the males (26 per cent) developed cutaneous reactions Among the patients showing skin reactions, the relative frequency of the various types were as given in Table 75 It will be noted that the experience of Paley and Tunbridge[19] agreed quite closely with that of Allan and Scherer[15] in this regard

In our own experience, fully one-fourth to one-third of patients show untoward skin responses at one time or another, not counting the mildest degrees of reaction

[13] Strauss Klin Wchnschr, 4, 491, 1925
[14] Wechsler, Farmer and Urban Jour Lab and Clin Med, 26, 1090, 1941
[15] Allan and Scherer Endocrinology, 16, 417, 1932
[16] Collens, Lerner and Fialka Am Jour Med Sci, 188, 528 1934
[17] Paley and Tunbridge Jour Pharm and Pharmacol, 2, 304, 1950
[18] Paley and Tunbridge Diabetes, 1, 22, 1952
[19] Paley and Tunbridge Loc cit p 307

the generalized reactions are accompanied by angioneurotic edema involving especially the loose tissues of the eyelids and lips When most severe, such reactions may in rare instances be accompanied by laryngeal edema and produce interference with respiration This type of generalized [illegible] alf hour after the insulin injection and [illegible] one to several hours. Occasionally [illegible] local reaction at the injection site followed in a few days or weeks by a general reaction, while still others as described by Watson[5] may have no reaction for several days followed by local reactions which increase in intensity until finally a generalized allergic response develops Epinephrine or ephedrine usually give relief but may need to be repeated frequently. Less frequent allergic responses have been those of gastro-intestinal symptoms,[6] non-thrombocytopenic purpura,[7] and various combinations of untoward effects.

Severe thrombocytopenic purpura developed in Constam's[8] patient a 65 year old man who had taken protamine zinc insulin for five years. With [illegible] rence of the purpura and an almost fatal outcome. Treatment with adrenocortitrophin followed by cortisone and return to unmodified insulin resulted in recovery. Tests of the patient's serum by the thrombocyte-agglutination test of Hoigné and Storck[9] and the nephelometric serological method of Hoigné, Grossman and Storck[10] gave positive results with protamine zinc insulin, lente and semilente insulin, "insulin pig glands" and protamine [illegible] insulin [illegible] blood [illegible]

Armstrong and Lloyd[11] reported the case of a 47-year-old man who after eleven days of treatment with an insulin zinc suspension, developed large bullae at the sites of injection and generalized malaise with anorexia and nausea Spontaneous desensitization occurred within three weeks In Gravano's[12] patient, diabetic coma requiring the use of 1250 units of insulin in 24 hours, developed after the intravenous administration of adrenocorticotrophin for severe urticaria which had followed the giving of protamine zinc insulin

The most serious allergic response to insulin is anaphylactic shock. Such reactions usually follow a period when insulin was omitted for a time and then resumed Unconsciousness, dyspnea, fall in blood pressure, and cyanosis, in addition to edema and urticaria may develop and the patient may appear moribund Fortunately no fatal cases have been reported, although one patient discontinued insulin because of severe allergy and

[5] Watson Canadian Med Assn Jour, 47, 336, 1942
[6] Bayer Jour Am Med Assn, 102, 1934, 1934
[7] Kern and Langner Ibid, 113, 198, 1939
[8] Constam Diabetes, 5, 121, 1956
[9] Hoigné and Storck Schweiz med Wchnschr, 83, 718, 1953
[10] Hoigné, Grossman and Storck Ibid, 85, 578, 1955
[11] Armstrong and Lloyd Brit Med Jour, 2, 396, 1954
[12] Gravano Dia Med, 27, 1859, 1955, Abst in Diabetes 5, 160, 1956.

died in diabetic coma [13] Case 26598 developed anaphylactic shock following the first injection of insulin she ever received but fortunately recovered, was desensitized and later received insulin without difficulty Wechsler *et al* [14] describe a sixty-five year old woman who had three such reactions, the first of which simulated a coronary occlusion

TABLE 75 —CLASSIFICATION OF DERMAL REACTIONS
(After Paley and Tunbridge)

1 Mild Local Reactions
  A Immediate
    [illegible]
  B Delayed
    Similar to the immediate reaction, but onset delayed 6 to 24 hours after injection
2 Severe Local Reactions
  A Immediate
    (1) Observed within 1 hour of injection
    (2) Area involved may extend to 15 cm in diameter
    (3) Usually disappears within a week
  B Delayed
    Identical with previous reaction, but onset delayed 6 to 24 hours after injection
3 Generalized Reactions
  Not encountered in series of Paley and Tunbridge
4 Pseudo-Reactions

Incidence —The incidence of untoward skin responses to insulin, as *noted by* various observers, has varied from *less* than *10* per cent[15, 16] to 55 8 per cent [17] The differences are due chiefly to the degree of care with which patients are examined following injections of insulin and whether or not one includes mild responses The high incidence reported by Paley and Tunbridge[18] was found in the diabetic clinic of the General Infirmary at Leeds, England, and concerned 147 patients who started treatment in the years 1947–1949 They noted that a larger proportion of the females (65 per cent) than of the males (26 per cent) developed cutaneous reactions Among the patients showing skin reactions, the relative frequency of the various types were as given in Table 75 It will be noted that the experience of Paley and Tunbridge[19] agreed quite closely with that of Allan and Scherer[15] in this regard

In our own experience, fully one-fourth to one-third of patients show untoward skin responses at one time or another, not counting the mildest degrees of reaction

[13] Strauss Klin Wchnschr, *4*, 491, 1925
[14] Wechsler, Farmer and Urban Jour Lab and Clin Med, *26*, 1090, 1941
[15] Allan and Scherer, Endocrinology, *16*, 417, 1932
[16] Collens, Lerner and Fialka Am Jour Med Sci, *188*, 528, 1934
[17] Paley and Tunbridge Jour Pharm and Pharmacol, *2*, 304, 1950
[18] Paley and Tunbridge Diabetes, *1*, 22, 1952
[19] Paley and Tunbridge Loc cit p 397

In contrast to the local manifestations of allergy, generalized reactions are rare. Paley and Tunbridge encountered none. Andreani and Corti[?] noted marked generalized reactions in only 3 of 1522 insulin-treated diabetics (0.2 per cent).

TABLE 76.—RELATIVE FREQUENCY OF EACH TYPE OF SKIN REACTION
(From Paley and Tunbridge[20])

Figures refer to percentages of total reactions

	Paley and Tunbridge[20]			Allan and Scherer[21]
Type of Reaction	Immediate per cent	Delayed per cent	Total per cent	Total per cent
Mild local	74.4	7.3	81.7	84.0
Severe local	17.1	1.2	18.3	12.0
Generalized	0.0	0.0	0.0	4.0
			100.0	100.0

Assuming that there are approximately 1.0–1.5 million known diabetics in the United States and that about 50 to 70 per cent of these take insulin,[23] it seems likely that at l[illegible] given daily. In proportion to [illegible] reported! At the New E[illegible] injections are given each year. In the years 1951–1957 there were 18,439 admissions of diabetic patients to the Joslin Clinic service at the New England Deaconess Hospital. About 90 per cent of the patients concerned [illegible]

[illegible] is
[illegible] is
a protein, (2) the protein characteristic of the animal from which the insulin was obtained, (3) impurities of a toxic nature not removed in the preparation of market insulin, (4) substances added to insulin, particularly those of protein character such as protamine or globin. Cases thought to illustrate each of these possibilities have been reported. However, Jorpes,[24] from the use of insulin preparations which have been recrystallized up to 7 times, concluded that the allergic reactions to insulin are not caused by insulin itself but by impurities. In a paper published in 1949 he stated that mixed beef and pork insulin recrystallized several times had been used successfully in Sweden during the preceding five years by about 300 diabetic patients who had shown local or general reactions to market insulin. All of these were able to use without any complications insulin subjected to multiple recrystallizations. Incidentally, about 80 per cent of the patients

[20] Paley and Tunbridge. Loc. cit., p. 397.
[illegible] 417, 1932.
[illegible] 315, 1954 (Abst. in Jour. Am. Med. Assn.,
[illegible] Medical Defense of the American Diabetes
[24] Jorpes. Loc. cit., p. [illegible]

were able later to take commercial insulin without difficulty These conclusions of Jorpes are in contrast to those of earlier workers, who thought that both humans and animals could be sensitized to the insulin molecule itself and demonstrate true allergy or anaphylaxis In this earlier work, sensitiveness in certain cases had been demonstrated with insulins from all companies and laboratories, and with insulin of all types derived from all sources, including crystalline and human insulins.[25] Hypersensitive response was demonstrated with as little as 1/2,000,000 unit of insulin However, it must be admitted that if these earlier studies had been carried out using insulin which had been subjected to repeated recrystallization, the outcome might have been different As Jorpes points out, in most studies little emphasis has been laid on the purity of the insulin Being a protein, insulin can be contaminated easily with other proteins and their split products, these impurities can be removed only by repeated recrystallization

As for the influence of substances added to insulin, it is true that in the [illegible]

for sterilization of the skin These reactions are less likely to occur if the insulin is given subcutaneously as is proper, instead of being given partly in the intradermal layers of the skin, as is sometimes done by error [26,27]

There is fairly general agreement that modified insulins, such as those containing protamine and globin, are more likely to yield allergic responses than is unmodified insulin. This has certainly been our experience Paley and Tunbridge state that in their patients dermal reactions occurred in 66 per cent of those [illegible]
cent of those given [illegible]
fewer skin responses [illegible]
taining protamine [illegible]
injections of protamine in 18 5 and native beef globin in 2 4 per cent of patients tested On the other hand, Kern and Langner,[29] using a suitable protamine test solution, performed skin tests on 104 diabetic patients taking protamine zinc insulin, of whom there were 17 patients experiencing local reactions with its use Kern and Langner tested also 100 non-diabetics who served as controls and also 8 allergic non-diabetic patients who were sensitive by skin tests to salmon muscle protein In all cases the results were negative To explain the frequent reactions with protamine insulins, where the addition of protamine to insulin seemed to increase the sensitivity to insulin, these authors made the interesting speculation that there was evidence that the addition to a true antigen of a substance possessing in itself no antigenic properties made sensitization to that antigen in an animal easier than the injection of the antigen alone

[25] Campbell, Gardiner and Scott Jour Clin Invest, *9*, 28, 1930
[26] Bryce Med Jour Australia, *1*, 371, 1933
[27] Kern and Langner Loc cit, p 396
[28] Page and Bauman Jour Am Med Assn, *124*, 704, 1944
[29] Kern and Langner Loc cit, p 396

Antibodies for Crystalline Insulin.—The existence of two antibodies for crystalline insulin was reported by Lowell[20,21,22] in two patients who had both insulin resistance requiring large doses of insulin and also sensitivity to injected insulin. The first antibody was thermostabile and insulin neutralizing capable of destroying the physiological effect of crystalline insulin. Mice injected with 0.5 cc. of such a patient's serum to which was added 0.02 units of crystalline insulin failed to develop hypoglycemia. When normal serum was substituted this amount of insulin regularly produced hypoglycemic convulsions. *In one human subject, the patient obtained a* marked insulin effect from 30 units of human insulin intravenously yet had little or no effect from 30 units of crystalline insulin. It was suggested that this insulin-neutralizing antibody accounted for the patient's resistance to crystalline insulin. Since the patient responded well to human insulin Lowell suggested that the part of the molecule which served as antigen for the neutralizing antibody was characteristic for insulin derived from beef and pork pancreas and was not the part of the molecule which acted physiologically as insulin. The second antibody was heat-labile and conferred sensitivity on normal skin as evidenced by passive transfer tests. The generalized urticaria which followed the injection of insulin was attributed to this antibody.

Nature of the Allergic Response.—*Characteristic of the majority of* the reported cases of hypersensitiveness to insulin having generalized reactions is the fact that these patients have received insulin in the past and it has been *omitted for a period* of weeks, months or years. With *resumption* [illegible] Bernstein [illegible]

to manifest itself, whereas such sensitization had been previously obscured by the frequent therapeutic (and incidentally desensitizing) injections." The appearance of allergic phenomena after resumption of insulin therapy [illegible]

tioned by several authors.

Although the usual thinking has been that sensitivity has been developed to insulin itself, it is entirely possible that the sensitivity seen is due to impurities in market insulin, particularly since most workers agree that, especially with crystalline insulin, there is no significant difference from [illegible] insulin or of products [illegible] subject, [illegible] ic manifestations, normal eosinophile count, and absence of a definite sensitizing period support the view that the dermal reactions to insulin are a local product in the solution and not a true allergic manifestation." As yet

20 Lowell. Proc. Soc. Exp. Biol. and Med., *50*, 167, 1942.
21 Lowell. Loc. cit., p. 400.
22 Lowell. Loc. cit., p. 400.
23 Bernstein, Kirener and Turner. Jour. Lab. and Clin. Med., *23*, 938, 1938.

no one has succeeded in identifying a specific impurity which is responsible for the dermal reactions

Eosinophilia.—When the routine admission blood smears of 293 con-

regular insulin and in 29.1 per cent of those using only protamine zinc insulin Except for 1 case with asthma and 1 case with eczema, no patient

treated with diet and insulin

ways

patient should certainly be encouraged to take insulin for several weeks in the hope that spontaneous desensitization will occur

have responded in this way.

Low Carbohydrate Diets.—The use of diets low in carbohydrate to

should hesitate before reducing the carbohydrate below 150 grams a day to avoid the use of insulin Only in rare cases where desensitization cannot

[34] Paley and Tunbridge Loc cit, p 397
[35] Collens, Lerner and Fialka Loc cit p 397
[36] Grishaw Jour Am Med Assn, *97*, 1885, 1931

ORAL HYPOGLYCEMIC AGENTS.—At first thought, it would appear logical to resort to oral hypoglycemic agents in patients allergic to insulin. However, this is defensible only in those patients with stable diabetes and a low insulin requirement. Those patients who really need insulin or for whom such need may be foreseen, should unquestionably receive it even at the expense of tedious desensitization. Otherwise, at some emergency in the future when insulin might be life-saving, costly time would be lost in the desensitization process.

"DENATURED" INSULIN.—Dolger[37] stated that in the treatment of local cutaneous reactions he had used successfully unmodified insulin which had been "denatured" by immersion of the vial of insulin in boiling water for 30 minutes. Favorable results were reported also with this procedure by Nichols[38] whose patient was an eleven-year-old girl with insulin allergy [illegible] to take market NPH insulin. Our experience with "denatured" insulin is not great enough to warrant a statement. However, in careful studies Loveless[39] was unable to substantiate Dolger's conclusion. She found that water-bath temperatures of 60 degrees centigrade maintained for 1 to 20 hours and of 100 degrees centigrade for 1 to 4 hours exerted little or no [illegible] -nd/or beef insulins [illegible] samples was only [illegible]

ANTIHISTAMINIC AGENTS.—In those patients in whom cutaneous reactions are severe and troublesome because of the extent of the swollen areas or the presence of urticaria, much aid in treatment may be obtained by the use of antihistaminic agents. Given orally in proper dosage they may tide the patient over a period of a few or several days until the processes of natural desensitization bring relief. In a certain few patients the injection of solutions of these substances along with insulin has proved effective.

DESENSITIZATION.—Patients who require desensitization are those sensi- [illegible] ...nses, [illegible] ian [illegible] ra- dermal desensitization, are easily obtainable. The usual method is to begin with a very small dose of diluted insulin and to increase rapidly the amount injected at frequent intervals as long as there is no significant local or general response. Should the latter occur one starts again from the last non-reacting dose. A wise procedure is to use crystalline insulin as the desensitizing agent.

[37] Dolger: New York State Jour. Med., *52*, 2023, 1952.
[38] Nichols: Jour. Pediat., *46*, 314, 1955.
[39] Loveless: Diabetes, 7, 278, 1958.
[40] Allan and Scherer: Loc. cit., p. 398.
[41] Bayer: Loc. cit., p. 396.
[42] Corcoran: Am. Jour. Med. Sci., *196*, 359, 1938.
[43] Ulrich, Hooker and Smith: New England Jour. Med., *221*, 522, 1939.
[44] Bryce: Loc. cit., p. 399.
[45] Herold: New Orleans Med. and Surg. Jour., *91*, 163, 1938.

The program of desensitization which we have usually followed calls for

1/125, the second day 1/100—1/50—1/25—1/12—and the third day 1/5—1/2—1—2 The first day's solution is prepared by placing 4 units of crystalline insulin under aseptic conditions in 40 cc. of normal saline and then further diluting by mixing 1 cc of the resulting solution with 9 cc. of normal saline. The final preparation contains 1/1000 unit of insulin in 1/10 cc of solution.

More rapid desensitization is entirely feasible Using the general plan just described, injections are made at 30 to 60 minute intervals If a point

Following desensitization there are sometimes unexpected findings Campbell *et al* reported that one patient developed local desensitization for only crystalline insulin on a part of only one thigh Allan and Scherer

insulin easily, but may still have positive skin tests,[48] or occasionally still have local reactions [49, 50] Desensitization may not be permanent, for after a period of regularly using insulin satisfactorily allergic symptoms may

blocking antibodies which compete with "allergic antibodies" present in

[46] Allan and Scherer Loc cit, p 398
[47] Baker Arch Int Med, *58*, 373, 1936
[48] Herold Loc cit, p 402
[49] Bayer Loc cit, p 396

9, 1935

conditions overlap the hormonally active area of the insulin molecule In such cases resistance to insulin would [illegible]

[illegible]

s [illegible] reactions until there [illegible] local reactions. Herzstein and Pollack[55] reported a case where an attempt at desensitization with histamine phosphate was not successful, and the patient was finally desensitized to protamine zinc insulin. Roth and Rynearson[56] reported a case where desensitization with histamine was successful.

Insulin Resistance.—Allergy to insulin and so-called insulin resistance may exist simultaneously.[57,58,59] Many patients with insulin resistance exhibit also allergy to insulin but only a very [illegible] allergy [illegible] doses of [illegible]

Lowe [illegible] bodies n [illegible] serum together, but need not vary in a parallel fashion

B. ALLERGIC STATES NOT PECULIAR TO DIABETES

Incidence of Allergic Conditions in Diabetics.—It was formerly believed that the ordinary allergic states are not frequently found in diabetic patients. Swern[61] found only 6 diabetics in a group of 4000 allergic patients, chiefly asthmatic, studied in a period of ten years Wilmer, Miller and Beardwood[62] had only 2 diabetic patients in [illegible]

[illegible] in which asthma was associated with low blood sugar values. By giving 100 grams of glucose he was able to reproduce the attacks, for when blood sugar values reached 48 to 64 [illegible] four [illegible] use o[illegible] feedi[illegible] have [illegible] fasting blood sugar and very definitely increased sugar tolerance.

In contrast to this view, Wagner and Rackemann[63] studied glucose

[54] Collins, Lerner and Fialka Loc cit, p 397
[55] Herzstein and Pollack Jour Mt Sinai Hosp, 6, 3, 1939
[56] Roth and Rynearson Proc Staff Meet Mayo Clin, 14, 353, 1939
[57] Glassberg, Somogyi and Taussig Arch Int Med, 40, 676, 1927
[58] Rudy New England Jour Med, 204, 791, 1931
[59] Goldner and Ricketts Jour Clin Endocrin, 2, 595, 1942
[60] Lowell Loc cit, p 400
[61] Swern Jour Allergy, 2, 375, 1931
[62] Wilmer [illegible] ed Jour, 29, 197, 1936
[illegible] 911

tolerance tests in asthmatics and concluded that the tests were normal for allergic cases and that whatever the fundamental nature of allergy

allergy seldom occur in the same patient only if the phrase, "at the same time," was added. His statistics demonstrated that the past medical histories of diabetics showed an even higher incidence of allergy than those of persons in the community at large Diabetic parents tended to have allergic children but allergic parents only infrequently had diabetic children Kern commented that this is what one would expect since diabetes is a

extent as non-diabetics

Asthma —Among approximately 18,439 diabetic admissions to the Joslin Clinic service at the New England Deaconess Hospital during 1951–1957 inclusive, the diagnosis of bronchial asthma was made in 69 cases It seems probable that some mild cases escaped tabulation due to failure to question the patient regarding allergic disease Both intrinsic and extrinsic asthma have been observed In some cases the asthma began years before the onset of the diabetes, and in others the reverse was true

In 1400 juvenile diabetics there were at least 11 with asthma In 6 cases the asthma began before the diabetes, in 2 after the diabetes, and in 3 cases the onset date of the asthma was not stated As with adults, the asthma was of both intrinsic and extrinsic types

Among diabetic patients with asthma requiring epinephrine, no significant permanent effect on the state of diabetic control has been noted Case 3717, a boy, aged fifteen years in 1923 when the diabetes began, had bronchial asthma since infancy The asthma was always severe and he was sensitive to the inhalants, eggs, milk, and other antigens. Attacks were almost of daily occurrence and he took from 4 to 24 injections of epinephrine (up to 0 8 cc. of 1 to 1000 solution) a day. He died August 10, 1947 of "insulin shock and bronchial asthma"

September 24, 1955, at the age of 69 years after 30 years of diabetes and asthma

[44] Kern Trans Assn Am Phys, 49, 23, 1934

Järvinen[97] analyzed data from a series of patients treated in 1934–48 in the Third Medical Clinic of the University of Helsinki and in the Medical Department of Kivelä Hospital. He found 5 patients with both bronchial asthma and diabetes mellitus. This constituted an incidence of 0.9 per cent of the 563 patients with asthma and 0.7 per cent of the 766 patients with diabetes. The average age in the group with asthma was 48.1 years and in those with diabetes, 51.6 years. Järvinen concluded that in his series, bronchial asthma and diabetes mellitus occurred together about as frequently as might be expected from morbidity figures of these diseases in the general population.

Miscellaneous Allergic States.—Hay-fever has been observed as an incidental finding in many diabetic patients. Hives, not due to hypersensitiveness to insulin has been noted, and has usually been due to sensitivity to certain foods. Diabetic patients have been observed with urticaria of serum disease, with eczema, with migraine of the common and the abdominal types, and with contact dermatitis due to drug sensitivity. There *is no reason to suppose that the incidence and course of these hypersensitivity reactions differ from those seen in non-diabetic persons.*

[97] Järvinen: Ann. Med. Intern. Fenn., 39, 210, 1950.

Chapter 15

CARDIOVASCULAR-RENAL DISEASE

HOWARD F. ROOT, M.D. and ROBERT F. BRADLEY, M.D.

General Considerations.—Further advances in our knowledge of the relation between diabetes mellitus and premature cardiovascular-renal dis-

nent and prevention
Observations upon
cially the vasomotor

indicate that the typical sequelæ in the eyes, arteries and kidneys may be postponed or prevented by early, persistent and continuous control of diabetes by proper diet and skillful use of insulin. Knowledge with regard to the site and mode of action of insulin, as well as to the interrelations of insulin action with that of other hormones and other metabolic regulators, is incomplete. Concentrated efforts are being made to explore basic aspects of carbohydrate, fat and protein metabolism in many tissues as well as their

Atherosclerotic changes in the first stages and of mild degree are easily discernible in many individuals as early as the second decade, whether the population studied is composed of diabetics or non-diabetics. It is the unusual frequency of advanced lesions of occlusive vascular disease, involving chiefly the coronary vessels, the leg arteries and the renal lesions pathognomonic of diabetes, which today provide the outstanding f...

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and
sclerosis obliterans will be considered in Chapter 25.

A. DISTRIBUTION OF CARDIOVASCULAR-RENAL DISEASE

The advancing average age of life expectancy in the United States and other countries with good vital statistics, together with improved diagnostic

methods, explain to a large degree the apparent great increase in the incidence of cardiovascular disease as a cause of death.[1] Cardiovascular diseases (including all types) caused 54 per cent of all deaths in the United States in 1956.[2] During the first 9 months in this same year, among 135 deaths of our diabetic patients, 113 or 83.7 per cent were due to arteriosclerotic cardiorenal-vascular disease without a single death from other circulatory or rheumatic heart disease. Even more striking is the fact that among 49,922 post-mortem examinations performed between 1910 and 1948, Bell[3] found 4 per cent of all deaths from conronary disease are associated with diabetes in males and 14 per cent in females. Gangrene was 40 times as frequent in diabetic as in non-diabetic females past 50 years of age. Severe renal arteriolosclerosis was 100 times as frequent in the diabetic as in the non-diabetic group. Of the 135 cases of childhood diabetes dying after more than ten years' duration, 72 died of nephritis.[4]

Criteria for the Incidence of Vascular Disease.—(1) The best criteria are obtained by autopsies, (2) next best by the certified causes of death on the death certificates of diabetics; (3) by clinical studies. Actually, certified causes of death are unreliable because 20 to 25 per cent of all diabetic patients escape designation as diabetics, since deaths occurring from coronary disease, or other causes, often are certified without the word "Diabetes" appearing at all on the death certificate. Evidence obtained from clinical physical examination, plus that by the roentgen ray, is important and the latter has been used with increasing frequency in recent years. Our physical examinations pay particular attention to the peripheral arteries by direct examination. The radial arteries are classified into four grades. (1) palpable, (2) roll under finger, (3) tortuous, (4) beaded or pipe-stem. Influence of increasing duration of diabetes upon the percentage of total deaths in diabetic patients, due to arteriosclerosis, has been a matter of record for years. During the Naunyn period, when the average duration of diabetes was only 4.9 years, only 17 per cent of the patients died with arteriosclerotic lesions. This percentage has increased steadily to 70 per cent during the period from 1944 to 1951. Actually, in the 1956 to 1957 period, when the average duration of diabetes reached 20 years and the age at death 65 years, arteriosclerotic lesions provided 77 per cent of the causes of death.

Evidence from post-mortem examinations summarized by Warren and LeCompte is given in Chapter 6. That the development of arteriosclerotic heart disease has become a major cause of death among diabetics generally, just as it has at the New England Deaconess Hospital, is confirmed by many writers and general hospital experience.

Clinical evidence of vascular disease is seldom apparent during the first two decades of life in the diabetic, because with present-day treatment practically no calcification of the arteries is visible and the lesions in the retinae are almost unheard of during that period. However, from the third decade onward, frequency and severity increase with the age, duration of

[1] Lew. Jour. Chronic Dis., 6, 192, 1957.
[2] World Almanac. New York World Telegram and Sun, New York, p. 307, 1958.
[3] Bell. Proc. Am. Diabetes Assn., 10, 62, 1950. Arch. Path., 53, 444, 1952.
[4] Joslin and Wilson. Brit. Med. Jour., 2, 1293,

the diabetes, and particularly through lack of good diabetic control. It is this final feature which has come to the fore in the last 5 to 10 years, emphasized by the observations at the Deaconess Hospital of Keiding, Root and Marble[5] and of Jackson[6] and his collaborators The series of approximately 400 patients studied at the Deaconess Hospital had the onset of diabetes in childhood and thereafter were followed up for study at periods [illegible]

those patients with diabetes under poorest control The same was true for retinal hemorrhages Twenty per cent of the patients with diabetes under [illegible]

The excessive duration of the degenerative changes in young diabetic patients, while possibly subject to genic influences, nevertheless is closely related not only to the duration of diabetes but the character of its control

B. THE PATHOLOGY OF DIABETIC VASCULAR DISEASE

The important diseases of the blood vessels in diabetes mellitus may be considered under three headings [7] (1) lesions of the larger arteries, that is, those included under the loose term of arteriosclerosis, (2) lesions of the arterioles, arteriolarsclerosis, and (3) lesions of the capillaries and venules

In considering the morphology of vascular disease found in the diabetic, one should remember that the peak in frequency for the development of diabetes is about 50 years of age, a period in life when susceptibility to vascular disease is greatest The peculiar features of diabetic vascular disease are seen in their purest and least complicated form in those patients whose diabetes has had its onset in childhood or very early life and who were studied after a duration of at least 10 to 15 years of diabetes It is in this group that the most advanced changes will be found, particularly in [illegible]

tion of the media, the Monckeberg type of sclerosis seen characteristically in arteries of the muscular type and particularly in the extremities in both diabetics and non-diabetics, is of great frequency in diabetics even early in life It is demonstrable by roentgen-ray with great ease even in young diabetics However one must remember that in the diabetic patient the presence of this calcification always means, sooner or later, the occurrence

[5] Keiding, Root and Marble Jour Am Med Assn, *150*, 964, 1952, Wilson, Root and Marble Am Jour Med Sci, *221* 479, 1951

[6] Hardin, Jackson, Johnson and Kelly Diabetes, *5*, 397, 1956, Jackson, Hardin, Walker, Hendricks and Kelly Proc Am Diabetes Assn, *9*, 307, 1949

[7] LeCompte Jour Chronic Dis, *2*, 178, 1955

of extensive atheromatous lesions together with the characteristic lesions in the smaller vessels

Diffuse intimal fibrosis or hyperplastic arteriosclerosis is the term used to describe a uniform increase of connective tissue in the arteries often associated with splitting of the elastic membrane. The condition occurs in both diabetics and non-diabetics and its relation to other forms seems not especially characteristic of diabetes.

Atherosclerosis is the focal lipid-containing type of arterial lesion, at present man's greatest killer. For discussion and bibliography, numerous reviews exist which may be consulted [8-11] The fact that diabetic patients usually develop atherosclerosis at an earlier age, in a more severe form than non-diabetics, has been documented many times, and no review of evidence will be attempted here. (See Chapter 6.)

Lesions of the arterioles consisting of medial hypertrophy, intimal fibrosis and intimal hyalization are found in varying combinations, particularly in the [illegible]
les[illegible]
ha[illegible]
important study of the kidney in 1,165 diabetic autopsies He concluded that in many cases arteriosclerosis may be attributed to the diabetic state, since it was present in over one-half of elderly diabetics without hypertension

Diseases of the smallest blood vessels, of the capillaries and venules, particularly in the kidney and the eye, seem almost pathognomonic of diabetes For discussions of the lesions of the eye, see Chapter 22, pp 547–552 and Chapter 6 for a discussion of the renal lesions

The pathology in the living must have its onset early during the course of diabetes or, if diabetes develops in the patients already having vascular disease, the accentuation and acceleration of further progression must take place rapidly Certain it is that some patients come to the physician with far-advanced retinal lesions and significant renal disease in whom the *history of diabetes indicates its origin within only* 3 to 5 years. It is well- [illegible] may [illegible] the [illegible] ssed later The incidence of coronary artery disease is vastly greater in diabetic women than in non-diabetic women, almost equalling the incidence in male diabetics and is well-documented by clinical studies and particularly by

[8] LeCompte Loc cit p 409
[9] Harper Arch Path, 38, 162, 245, 1944, 39, 117, 1945
[10] Duff and McMillan Am Jour Med, *11*, 92, 1951
[11] Katz and Dauber Jour Mt Sinai Hosp, *12*, 382, 1945
[12] *Gould* Am Jour Med, *11*, 209, 1951
[13] Jones *et al* Ibid, p 458
[14] Russ, Eder and Barr Ibid, p 468
[15] Adlersberg Ibid, p 600
[16] Davidson Ibid, p 730
[17] Katz and Stamler Experimental Atherosclerosis, Springfield, Ill., C. C Thomas, 1953
[18] Page Circulation, *10*, 1, 1954

autopsies [19-23] Coronary artery disease is now the leading cause of death in diabetic patients For discussion of the diabetic nephropathy see p 429 The incidence of myocardial infarction with a clinical history of angina is great in patients whose symptoms had begun with diabetic nephropathy Myocardial infarction occurs in diabetic patients with an extraordinary incidence [24-27] Martensson recorded an incidence of coronary atherosclerosis in diabetic patients of 43 per cent after 15 years of the disease.[28] In our experience at the New England Deaconess Hospital the incidence of angina pectoris and coronary arteriosclerosis doubled in the second decade of the disease. The incidence of premature severe vascular lesions in the smaller arteries of the eyes, kidneys and even the atherosclerotic changes in large arteries, is related closely to the quality of treatment, and today the prevention of such lesions in diabetic patients under proper treatment with early, continuous use of insulin, adequate dietary provision, and continuous good medical supervision can be predicted

C. ETIOLOGY OF CARDIOVASCULAR-RENAL DISEASE

Introduction—Although possibly metabolic factors in the development of premature atherosclerosis and degenerative changes in arterioles, venules and capillaries are of chief concern to the diabetic, other factors known to influence the incidence and course of vascular disease must be considered Inevitably, the problem of the degenerative and sclerosing arterial diseases known under the collective term of arteriosclerosis is concerned with the processes of senescence However, causes other than senescence, thought to be operative in the development of vascular disease, may have been operative before diabetes began or concomitant after its onset Among such factors may be mentioned various toxins of bacterial or other origin, anoxemia, various mechanical traumata, and heredity.

Among the factors influencing the arterial system, the autonomic nervous system and central nervous system must be considered because of their influence upon vascular tone and particularly upon hypertension Here [illegible]

action on the media and other relationships The influence of the pituitary gland, the female sex hormones and the thyroid are difficult to assess in this complicated problem Obesity, lipid content of the diet and hypercholesteremia, either hereditary or acquired, have been emphasized The massive

[19] Root and Sharkey New England Jour Med, *215*, 605, 1936
[20] Nathanson Am Jour Med Sci, *170*, 240, 1925
[21] Root, Bland, Gordon and White Jour Am Med Assn, *113*, 27, 1939
[22] Lisa, Magiday, Galloway and Hart Ibid, *120*, 192, 1942
[23] Millard and Root Am Jour Digest Dis *15* 41, 1948
36
305, 1949
1952
7, 1956

of extensive atheromatous lesions together with the characteristic lesions in the smaller vessels

Diffuse intimal fibrosis or hyperplastic arteriosclerosis is the term used to describe a uniform increase of connective tissue in the arteries often associated with splitting of the elastic membrane. The condition occurs in both diabetics and non-diabetics and its relation to other forms seems not especially characteristic of diabetes.

Atherosclerosis is the focal lipid-containing type of arterial lesion, at present man's greatest killer. For discussion and bibliography, numerous reviews exist which may be consulted.[8-18] The fact that diabetic patients usually develop atherosclerosis at an earlier age, in a more severe form than non-diabetics, has been documented many times, and no review of evidence will be attempted here. (See Chapter 6.)

Lesions of the arterioles consisting of medial hypertrophy, intimal fibrosis and intimal hyalization are found in varying combinations, particularly in the kidney with long-standing hypertension. The great frequency of these *lesions in diabetic patients, even in early life, with diabetes of long duration,* has been reported often This has been brought out especially by Bell's important study of the kidney in 1,465 diabetic autopsies He concluded that in many cases arteriosclerosis may be attributed to the diabetic state, since it was present in over *one-half of elderly diabetics without hypertension*

Diseases of the smallest blood vessels, of the capillaries and venules, particularly in the kidney and the eye, seem almost pathognomonic of diabetes For discussions of the lesions of the eye, see Chapter 22, pp. 547–552 and Chapter 6 for a discussion of the renal lesions.

The pathology in the living must have its onset early during the course of diabetes or, if diabetes develops in the patients already having vascular disease, the accentuation and acceleration of further progression must take place rapidly Certain it is that some patients come to the physician with far-advanced retinal lesions and significant renal disease in whom the *history of diabetes indicates its origin within only 3 to 5 years* It is well-known that diabetes, particularly when involving the smaller vessels, may be slowly but surely progressing. Whether or not factors in addition to the metabolic disturbance of diabetes itself are of importance may be discussed later. *The incidence of coronary artery disease is vastly greater in diabetic* women than in non-diabetic women, almost equalling the incidence in male diabetics and is well-documented by clinical studies and particularly by

[8] *LeCompte Loc cit p 400*
[9] Hueper Arch Path, 38, 162, 215, 1944 *39*, 117, 1945
[10] Duff and McMillan Am Jour Med, *11*, 92, 1951
[11] Katz and Dauber Jour Mt Sinai Hosp, *12*, 382 1945
[12] Gould Am Jour Med, *11*, 209, 1951
[13] Jones *et al.* Ibid, p 358
[14] Russ, Eder and Barr Ibid, p 468
[15] Adlersberg Ibid, p 600
[16] Davidson Ibid, p 736
[17] Katz and Stamler Experimental Atherosclerosis, Springfield, Ill, C C Thomas, 1953
[18] *Page Circulation, 10, 1, 1954*

and is completely or partially reversible by *adequate* insulin, and (3) a vas-
[illegible]

findings now available

[illegible]

ever, experience with the exceptional diabetic peculiarly susceptible or resistant to vascular disease does not justify disregarding results found in the majority of diabetics, in whom control and duration of diabetes are the major factors

(*b*) *Changes in Small Blood Vessels of the Bulbar Conjunctiva* —Until re-
[illegible]

capillaries and venules, arteriolar constriction, and slowed blood flow with intravascular erythrocyte aggregation

This characteristic pattern is seen in children with incipient diabetes long before retinopathy is detected, and becomes increasingly frequent and severe with the increasing duration of diabetes[54] and recognized retinopathy[55] A significant relationship has been found between the abnormal conjunctival pattern and the degree of small blood vessel disease, regardless of the duration of diabetes Hence, abnormal vasomotor changes may play an important role both in the development of diabetic retinopathy and diabetic nephropathy[56]

Conjunctival abnormalities are aggravated during the third trimester of pregnancy and by poorly controlled diabetes, when associated with elevations in serum protein-bound carbohydrate and beta lipoprotein[57] How-

[54] Ditzel, White and Duckers Diabetes 3, 99, 1954
[55] Ditzel Loc cit p 412
[illegible], 1957
[illegible]3, 1956
[illegible]Med , *101*, 912, 1958

data compiled giving the pros and cons of the concept that a high fat intake, particularly that of animal origin, leads to abnormal lipid levels and in turn to atherosclerosis and vascular occlusion has been adequately summarized elsewhere.[32-39]

Etiology of Small Vessel Disease in the Diabetic.—*Involvement of venules, capillaries and arterioles is now considered the most characteristic feature of vascular disease in the diabetic. It may be wide-spread. Changes* [illegible] n,[41] pancreatic islets,[42] and placenta, [illegible] polysaccharide deposition and en- [illegible] Diabetic "microangiopathy"[40] has been described as the common denominator in most forms of vascular disease. Its important role is suggested by (1) marked vulnerability of the skin of the diabetic to injury and infection, (2) extreme capillary fragility in distal portions of the extremities, (3) intensity and general distribution of arteriolar sclerosis, (4) microplethysmographic demonstration of diminished blood flow in the toes previous to signs of obliterative intimal disease,[44] and (5) tendency for coronary heart disease to result in myocardial rupture or repeated infarction.[45] The changes may be described as follows:[46] (1) impairment of circulatory flow in terminal vessels leading to prolonged hypoxia and undernutrition of the endothelium,[47,48] and (2) a metabolic disorder of simple polysaccharides (glycogen) or complex polysaccharides (mucopolysaccharides) or both, involving basement membranes of capillaries and ground substance of connective tissue.[49,50] Morphology of the lesions, and evidence they contain lipid and mucopolysaccharide material, are presented in detail in Chapter 6 and in a recent summary.[51]

Despite uncertainty as to whether this change takes place first in the wall of the small vessel or in the metabolites circulating through it, at least three major etiologic concepts ar[illegible]
disturbed metabolism, *controllabl*[illegible]
underlying vascular disturbance [illegible]

[32] [illegible] 223, 1957
[33] [illegible], *164*, 1890, 1957
[34] [illegible] arson, Keys Ann Int Med, *48*, 83, 1958
[35] [illegible] 7, 2313, 1957.
[36] [illegible] n, *16*, 163, 1957.
[36] [illegible]
[37] [illegible] sclerosis Circulation, *14*, 691, 1956
[38] Yudkin Lancet, *2*, 155, 1957
[39] Ahrens Am Jour Med, *23*, 928, 1957
[illegible]

[illegible], 96, 1957.

Although no *primary* disturbance in lipid metabolism associated with diabetes has been proven, increased non-esterified fatty acid (NEFA) levels in the "controlled" diabetic have been reported[63] However, it is not clear whether this or any other defect can be shown prior to the development of recognizable vascular disease, during normal control and carbohydrate utilization

MECHANISM.—Blood lipids increase as a result of fat ingestion[64] with peak levels usually reached at from 1 to 6 hours when they return rapidly to normal Prolongation of the disappearance curve for fat, after somewhat higher maximum concentrations, has been noted in the diabetic.[65] On occasion lactescence occurs, but lipemia as high as 4 4 per cent total lipid, Case 310, does not necessarily give a milky appearance

"Transport hyperlipemia" of uncontrolled diabetes has been explained through the finding of reduced fatty acid synthesis after a brief period of starvation and its reversal after carbohydrate ingestion[66] Reversal of diminished fatty acid synthesis in diabetic tissues by means of insulin has been shown repeatedly with the use of labelled substrates (See Chapter 4) Insulin deficit results in (1) decreased, long-chain fatty acid synthesis in the liver, and (2) decreased metabolism of fatty acid in peripheral depots In the first defect, increased cholesterol synthesis occurs and in the second, circulating esterfied fatty acid and NEFA[67] are increased Ketone production is greatly enhanced by a combination of both

Dole[67] gives calculations for the occurrence of *measurable ketosis* as follows. maximal output of ketones from the liver of a diabetic cat (equivalent to ±2 3 gm fat per kg body weight per day)[68] is greater than total turnover of neutral fat in normal liver (equivalent to ±1 5 gm fat per kg body weight per day)[69, 70] and peripheral tissues oxidize ketones at a rapid rate (equivalent to 2 5 gm fat per kg body weight per day) without the appearance of ketosis[67] Therefore, if ketosis is to be measurable, fatty acid from depots must flood the liver Clinically these observations indicate that insulin deficits can produce abnormally elevated circulating lipid fractions at a time when demonstrable ketosis has not yet occurred

(*a*) *Total Lipids*—No single factor creates a disturbance in lipids com-

phospholipids also occur[71–73] Gross hyperlipemia has been observed repeatedly, especially in the preinsulin era with blood fat concentrations

[63] Bierman, Dole and Roberts Diabetes, *6*, 475, 1957
[64] Man and Gildea Jour Biol Chem, *99*, 61, 1932
[65] Blotner Medical Papers dedicated to Henry A Christian, Baltimore, Waverly Press, p 450, 1936
[66] Stetten and Boxer Jour Biol Chem, *156*, 271, 1944
[67] Dole Bull New York Acad Med, *34*, 21, 1958
[68] Stadie Ibid, *19* 778, 1943
[69] Harper *et al* Metabolism, *2*, 62, 1953
[70] Handbook of Biol Data, edited by W S Spector Philadelphia, W B Saunders Co Tables 55, 133, 1956
[71] Herbert Biochem Jour, *29*, 1887, 1935
[72] Harris, Albrink, VanEck, Man and Peters Metabolism *2*, 120, 1953
[73] Man and Albrink Yale Jour Biol and Med, *29*, 316, 1956

ever, they are not binding with pregnancy or long duration diabetes, and may be reversible within a few hours by improved control of diabetes with insulin[58]

Children of diabetic mothers showed abnormal conjunctival vascular patterns in 35 to 43 per cent of those studied.[59] Most of those showing vascular changes were found to have hyperglycemic glucose tolerance tests, but over a 3 year period, three children with normal carbohydrate tolerance developed overt diabetes Ditzel, White and Sargeant concluded the results indicated that degeneration of smaller blood vessels in the diabetic was related to abnormal vasomotor responses and disturbances in carbohydrate metabolism.

(c) *Circulating Lipid, Protein and Carbohydrate Fractions*—Abnormalities in levels of lipid, lipoprotein, protein, and protein-bound carbohydrate fractions occur with uncontrolled diabetes. With few exceptions these are dramatically reversed in the early stages by improved control of diabetes with diet and insulin In the presence of nephropathy and retinopathy, such abnormalities tend to become irreversible Although there is no good evidence to prove that circulating sugar *per se* is responsible, an increased blood sugar level is an indication of insufficient insulin and inadequate

may have a significance similar to that of abnormal conjunctival vascular patterns, as either or both may contribute to the development of lesions in blood vessels, or merely serve as indicators of an injurious process In either event, these changes are of increasing importance due to correlation with the effectiveness of diabetic treatment

Etiology of Atherosclerosis in the Diabetic.—Diabetes increases the intensity, extent, and incidence of atherosclerosis. Although the morphologic changes appear similar, Lundbaek and Petersen[60] report that lipid composition of coronary arteries and rate of incorporation of P_{32} into blood phospholipids[61] are not the same in diabetics as in non-diabetics Although small vessel lesions have not been demonstrated in the "vasa vasorum" of

may be multiple

Circulating Lipids in the Diabetic—Changes in circulating lipid and protein fractions are related to vascular disease in the diabetic It is uncertain whether or not they actually produce small vessel disease or atherosclerosis, or are merely indicators of damage to blood vessels presently occurring or already in progress

[58] Ditzel and Camerini-Dávalos Proc Soc Exp Biol and Med, *97*, 475, 1958
[59] Ditzel, White and Sargeant Acta Genetica et St Med, 7, 101, 1957.
[60] Lundbaek and Petersen Acta Med Scand, *144*, ..., 1953
[61] Christensen, Jensen and Lundbaek Jour Clin Lab Invest, 7, 212, 1955
[62] Warren and LeCompte Loc, cit, p 170

Cholesterol is actively synthesized[88] by the liver. The exact amount is still undetermined, but possibly 90 per cent of the total body cholesterol may have been so synthesized The human intake of 1 0 gm or less per day and its slow rate of absorption[89] would support this figure The metabolic fate of ingested cholesterol is indistinguishable from that which is synthesized endogenously.

No characteristic increase in blood cholesterol occurs after fat ingestion and under constant conditions significant changes (less than 20 per cent) occur infrequently. It serves as a rough measure for levels of low density and beta-lipoproteins but not of triglyceride, chylomicra, or NEFA.

There is poor numerical correlation between cholesterol and blood sugar values Extreme examples have been seen One patient, Case 12383, with *a blood cholesterol of 1600 mg. per cent* and lipemia retinalis, had a blood sugar of 210 mg per cent. On the other hand, 2 patients, Cases 4099, 6884, had the highest blood sugars, 1600 and 1580 mg per cent, with cholesterol values of 370 and 348 mg. per cent respectively. Both of these recovered.

ally accepted Present maximum figures may need downward revision For a man age 40 to 50 years levels should not exceed 240 mg per cent, and below this age 220 mg per cent would be safer For women in the same age bracket it is 15 to 20 mg per cent less [90] "Desirable" levels may be lower still

In recent years cholesterol determinations have not been done routinely, *but only for those patients in whom abnormal values might be expected* Despite this, the average values obtained are comparable to the statistical average for the years 1932–1939 See Table 54

1 *High Values in Diabetes* —Experience of the Joslin Clinic has indicated

practical purposes a cholesterol consistently above 400 mg per cent in a diabetic implies that serious complications exist or are imminent

2 *Response to Insulin* —Cholesterol content of blood from normal people does not respond to insulin, but the hypercholesterolemia of experimental and clinical diabetes is reduced,[91 92] though it is less rapidly responsive to insulin[93] than other lipid moieties

J, 1920, 1957.

ranging from 15 to 27 per cent as in parentheses. (Case 9629). Hyperlipemia with essentially mild diabetes has been associated with advanced vascular disease.[71] Excessive fat is found in the blood of the uncontrolled diabetic regardless of how low the fat intake may be. Cholesterol values may be high or low in both creamy (75-1600 mg. per cent)[73] and clear sera.

Reduction of hyperlipemia in a diabetic following administration of insulin has occurred in from several hours to several days, Cases 9629, 12383, 12384. The patient reported by Rabinowitch[76] lost a pound of fat from the blood overnight and another pound the next day after intensive insulin therapy. Even though fat intake is liberal, the blood lipid levels of the diabetic fall when adequate carbohydrate utilization is insured.[77,78]

(*b*) *Esterified Fatty Acid.*—Elevated fasting esterified fatty acid levels with increased peak rise after fatty meals, and delayed return to fasting levels have been noted in diabetics by Hirsch and Carbonaro.[79] They correlated the degree of lipemia with blood sugar elevations and found rapid restoration of both to normal after insulin.[80,81]

(*c*) *Non-esterified Fatty Acid (NEFA)*—As triglyceride is hydrolyzed from chylomicra and lipoproteins, the fatty acids liberated are transported in combination with albumin in the fast-moving stream of non-esterified fatty acid (NEFA). Although forming a small fraction in terms of 5 per cent of serum fatty acids, their turnover rate is so great that more than twice as many calories (80 to 100 per cent of total) may be delivered to tissues as is derived from glucose.[82] NEFA levels in plasma fall[83,84] after administra- ... ie or glycagon[85] ... acid and occur ... In the normal person and *responsive* diabetic tolbutamide produces a fall in NEFA closely ...

(*d*) *Cholesterol*—Chemically, cholesterol is not a lipid, but its cyclopentenoperhydrophenanthrene nucleus (common to steroids, vitamin D, and bile acids) keeps inserting itself into the lipid picture. About 60 to 70 per cent is esterified with fatty acid and is transported in greatest concentration as low density or beta-lipoprotein

[73] Adlersberg and Wang Diabetes, 4, 210, 1955

[74] Joslin *et al* Treatment of Diabetes Mellitus, 9th ed, Philadelphia, Lea & Febiger, P 165, 1952

... 1936

... , 496, 1957.

... 1957.

acute and chronic effects of a gross insulin deficit in the long unrecognized or uncontrolled diabetic first seen in acidosis with xanthomatoses, lipemia retinalis, creamy serum and gross elevations in all blood lipids Shortly after this study ended no clinical or laboratory evidence of lipid abnormality could be detected

Recently, sequential studies done in an older man, Case 49204, with a similar clinical picture have shown by the *electrophoretic* technique grossly elevated beta-lipoprotein and cholesterol fractions which responded rapidly to diet and insulin Figure 22 illustrates the degree and rapidity of these changes

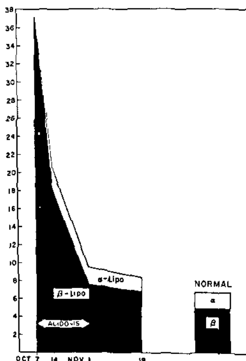


FIG 22 —Return of elevated lipoprotein levels toward normal during and following treatment of diabetic ketoacidosis α—lipo-Alpha lipoprotein. β—lipo-Beta lipoprotein

In the absence of grossly uncontrolled diabetes S_f 10–20 lipoproteins,

[102] Gofman *et al* Gerontology, *6*, 105, 1951
[103] Kolb *et al* Amer Jour Med, *15*, 417, 1953
[104] Gofman Educ Proc Permanente Hosp, *2*, 174, 1952
[105] Barach and Lowy Diabetes, *1*, 441, 1952
[106] Lowy and Barach Ibid, *6*, 342, 1957

Elevated cholesterol is seen frequently in new, untreated cases of diabetes, but within a few weeks after adequate treatment with diet and insulin repeated determinations usually show normal levels. The response to insulin and adequate carbohydrate intake is in most instances complete, while restriction of fat in the diet has very little effect, unless the diabetes is controlled.

Diabetic children under "good control" have cholesterol, phospholipid, and fatty acid values comparable to normal children.[94] In the absence of acidosis or complications similar findings have appeared in the majority of patients studied by Man and Peters,[95] and in a recent series of diabetics no significant cholesterol elevations were found.[96]

Pomeranze and Kunkel[97] noted ±50 per cent of 273 diabetics showed total lipids in excess of 750 mg. per cent (upper limit of normal), including rises in neutral fat, cholesterol, and phospholipid. Severity, duration, or control of the diabetes seemed not important, but criteria for "control" are not stated.

Recently, lipid levels in diabetic children taken simultaneously with blood sugar determinations illustrate the possible importance of accurately defining "control of diabetes" in a more specific manner. Wolff and Salt found lower mean levels of beta lipoprotein lipid, cholesterol, and esterified fatty acid at times when blood sugar levels were 200 mg. per cent or less than when they exceeded this figure.[98]

TABLE 77.—SERUM LIPOPROTEIN VALUES IN DIABETIC LIPEMIA

Day	*Sf 12-20 mgs Per Cent*	*Sf 21-35 mgs Per Cent*	*Sf 36-100 mgs Per Cent*	*Cholesterol mgs Per Cent*
1	34	72	305	1116
4	290	280	490	1235
8	370	285	295	476
45	32	8	5	391

3. *Lipoproteins.*—The degree of elevation of serum lipids is clearly related to the severity of ketoacidosis in cases studied at the New England Deaconess Hospital. In 18 patients lipoproteins and cholesterol of the serum were increased to higher levels in patients with plasma values below 9 mm. than in cases with CO_2 values from 9 to 15 mm., in the report of Tuller *et al.*[99] The elevated S_f 12-20 lipoprotein fractions determined by the ultracentrifugal method responded dramatically to insulin by falling toward normal levels, but the transfer of low density material to higher density fractions resulted in temporary rises. Table 77 shows this sequence of events in an 18 year old boy (Case 39428), and the ultimate normal values attained, with the exception of cholesterol (391 mg. per cent) at 45 days after adequate treatment started. He is a classic example of the

5, 116, 1956

954.

ketoacidosis is associated with a high blood sugar and glycogen storage disease with a low one, but both are characterized by inadequate carbohydrate utilization Kolb, deLalla, and Gofman[115] suggest that any degree of uncontrolled diabetes has a corresponding effect both on lipoprotein pattern and the development of atherosclerosis, and it is reasonable to postulate that a similar series of events may be involved in the production of small vessel lesions

4 *Serum Proteins and Protein-Bound Carbohydrates**.—Electrophorectic

Increase in gamma globulin fractions has been observed in patients with resistance to insulin,[126 127] and electrophoresis of the sera from 30 out of 70 of our own diabetic patients revealed significantly elevated gamma globulin [128]

reversible abnormalities may be brought about within a few days, but the lowered total proteins and albumin, elevation of $alpha_2$ and beta globulins, and the occasional elevation of gamma globulins become more pronounced in their deviation from normal and are irreversible once extensive vascular lesions, such as diabetic nephropathy, have developed

*Based on data kindly supplied by Pierre Moinat, M D, George F Baker Clinic Research Laboratory, New England Deaconess Hospital, Boston

4, 535, 1944
1946

the cholesterol values have as much significance as S_f 12-20 or S_f 2-1000 lipoproteins, and that all 3 fractions tended toward higher figures in all diabetics with poorer grades of diabetic control. Generally, white female diabetics had higher S_f values, particularly striking in those women with retinopathy, atherosclerosis and hypertension.

Although abnormal lipoproteins have been confirmed in diabetics with[105-107] and without[108] vascular disease, and abnormalities related only to atherosclerosis are denied,[109, 110] elevated lipids are confirmed repeatedly in diabetic patients with nephropathy[111,112] and in one instance with retinitis.[113]

Determination of S_f 12-20 lipoproteins in diabetic patients of the Joslin Clinic has been performed through the courtesy of Dr. Frederick J. Stare and Dr. George V. Mann. The results are reviewed by Keiding, Mann, Root, Lowry and Marble[111] and by Mann.[114] Data upon 144 of the patients

TABLE 78.—SERUM LIPOPROTEIN VALUES IN DIABETES ACCORDING TO CONTROL.
144 cases with onset of diabetes between 1 and 20 years of age

Control	Duration years	Cases	S_f 12-20 mg. per cent	S_f 20-35 mg. per cent	S_f 35-100 mg. per cent	Serum cholesterol mg. per cent
Good	10-18	10	31	17	25	223
	19-31	9	33	15	21	211
Fair	10-18	18	41	22	26	229
	19-31	11	43	17	29	231
Poor	10-18	50	52	31	42	218
	19-31	46	50	31	48	206

are summarized in Table 78. It can be said that the diabetic group which included only patients with onset of diabetes early in life and with duration of diabetes exceeding 10 years show on the whole a higher S_f 12-20 level than normals. There is a definite tendency for the occurrence of increasing concentrations in patients with marked diabetic complications such as retinitis and poor control of the diabetes. The actual interpretation of single readings requires careful analysis of the patient's record since it is true that in the presence of slight acidosis or poorly controlled diabetes rapid changes in the level of lipoproteins may occur, especially under the influence of treatment with insulin and diet.

[105] Nikkila: Scand. Jour. Clin. Lab. Invest., 5, Suppl. 8, 1953.
[106] Swahn: Ibid., suppl. 9.
[107] Baker, Joiner and Trounce: Quart. Jour. Med., 24, 96, 1955.
1, 468, 1951.
Scand., 148, 417, 1954.
m. Med. Assn., 158, 814, 1954.
1, 425, 1952.
Ibid., 1, 434, 1952.
[113] Kolb, deLalla and Gofman: Metabolism, 4, 310, 1955.

5 *Protein-Bound Carbohydrates*.—Carbohydrate is present in the living organism in the free and conjugated forms. When free it is used as fuel, and when conjugated it is part of specific structures. When ... tains more hexose as part of specific structures. H ...

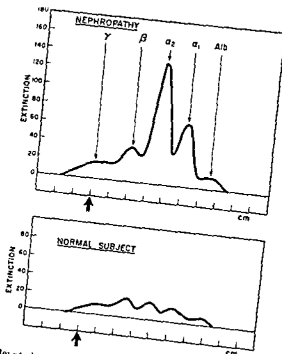


Fig. 25 Elevated protein-bound carbohydrates in the serum of a diabetic subject with nephropathy. Densitometric curves of stained carbohydrates bound to the albumin and globulin fractions. γ = Carbohydrate bound to gamma globulin. β = Carbohydrate bound to beta globulin. α_2, α_1 = Carbohydrate bound to alpha globulin. Alb = Carbohydrate bound to albumin.

substances such as hyaluronic acid, sulfated mucopolysacch... supporting tissues, heparin, mucoprot... all protein-bound carbohydrates ... data is available, but their func... ways, and possible relation to diabetic vascular disease is obscure. However, MacManus[110] has postulated that increased quantities of protein-bound carbohydrate in the

[illegible] Calkins, Saodik and Bauer, New England Jour. Med., *253*, 865, 1955.
[110] McManus, Proc. Am. Diab. Assn., *9*, 303, 1949.

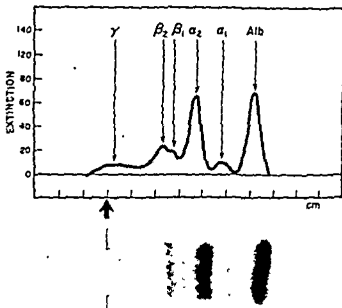


FIG 23 Serum protein changes in diabetes with extensive vascular lesions (Triopathy) Lowered total proteins, lowered albumin and important increase of alpha, globulins γ = gamma globulin β_2, β_1 = beta globulin α_1, α_2 = alpha globulin Alb = albumin

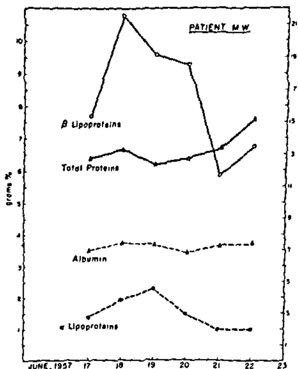


FIG 24 --Effect of insulin on serum proteins and lipoproteins Increase of total proteins and albumin, and decrease of alpha and beta-lipoproteins (Left scale in gms. per cent for proteins and right scale in arbitrary units for lipoprotein figures)

cent, retinopathy in 60 per cent, and hypertension in 65 per cent. This led to his conclusion that control of diabetes by diet restriction should be carried out. Dunlop[134] and Matthews[135] found a significant increase in incidence and severity of vascular complications for those diabetics who had poorest control of the metabolic condition and have affirmed the importance of [illegible] [136] [illegible] patients and at the end of 20 to 29 years classified their conditions in relation to the type of treatment which had been carried out. Unfortunately, as follow-up studies indicated, these youthful patients had not been under [illegible]

which had been weighed or carefully measured throughout the 20 years, (3) daily testing of the urine with adjustment of the insulin dose to secure at least part of the time, sugar-free urine specimens; (4) regular medical [illegible]

percentage of patients with good control showing significant calcification of peripheral blood vessels was a fraction when compared to the frequency in patients with poor control by roentgen-ray examination. The incidence [illegible]

quality of treatment rather than the duration of diabetes which has major effects upon the incidence of the severe vascular lesions. Finally, the most significant results are shown in the series of Victory Medal patients reported by Joslin. In this series (now 82 patients), complete freedom from retinitis, or from roentgen-ray evidence of calcified vessels, is found in patients whose diabetes has existed for 25 years or more. These patients have shown consistently the following features: The use of insulin from the onset of diabetes, the daily attempt to control glycosuria, continuing good medical supervision.

The basic biologic and biochemical factors in the causation of retinitis and renal lesions are, as yet, not well defined. It is clear that the early and continuous use of insulin and adequate diet with good medical supervision regularly carried out does control these unknown factors. Today, we have a new confidence that the early and persistent use of measures now well-known to physicians, together with continuous efforts to extend information

[134] Dunlop: Brit. Med. Jour., 2, 383, 1954.
[135] Matthews: Lancet, 2, 574, 1954.
[136] Wilson, Root and Marble: New England Jour. Med., 245, 513, 1951.
[137] Hardin, Jackson, Johnston and Kelly: Diabetes, 5, 397, 1956.

blood are responsible for excessive deposits in certain tissues, and the same material may be detected in vascular lesions of advanced diabetes as is found in the blood.

Using electrophoretic separation of the serum from diabetic patients with vascular lesions and staining the carbohydrate part of each fraction with fuchsin sulfite has revealed elevated serum levels of hexosamine and non-hexosamine components on comparison with sera from normal individuals.[131,132] The marked elevation in bound hexoses seen in a diabetic subject with nephropathy is illustrated in Figure 25, the greatest change occurring in the hexoses bound to the $alpha_1$ and $alpha_2$ protein fractions

The principal features in the behavior of protein-bound carbohydrates in diabetic subjects are several: (1) higher mean levels of total and $alpha_2$ protein-bound carbohydrate, (2) a wider variation of these levels than is seen in normal subjects, (3) rising levels of hexoses bound to serum protein with extensive tissue lesions (mainly vascular), and (4) the tendency for increased protein-bound carbohydrate to be transient and reversible early in the course of diabetes and to be permanent when vascular disease is established (nephropathy)

Summary.—Atherosclerotic and small vessel disease is intimately associated with metabolic abnormalities in the diabetic. Such abnormalities may be the cause or merely play a "permissive" role in allowing progression of accompanying abnormal vascular responses Restoration of carbohydrate utiliz

single agen

producing ,

lipoproteins, proteins and protein-bound carbohydrates remain reversible in most instances until late complications of diabetes are detectable.

Lacking accurate means to measure the individual factors which determine the diabetics' susceptibility to small vessel disease or atherosclerosis, preventive measures must consist of control of diabetes and hypertension, and cautious attempts to reverse atherogenic lipid patterns

D PREVENTION AND TREATMENT OF VASCULAR DISEASE IN DIABETES

Preventive measures hold great promise for the future. Continuing efforts to control diabetes, especially in those with onset of diabetes in youth and early life, is the prime object In patients of older age, 40 years or later, treatment of factors important in the genesis of atherosclerosis, particularly hypertension, must be emphasized together with control of diabetes. An increasing array of follow-up studies over long periods of time, concerned with patients whose onset of diabetes has occurred early in life, give convincing evidence in support of these conclusions Engelson[133] reported a disastrous number of vascular lesions in patients with diabetes for ten years or less when treated with "free diet " Nephropathy was present in 65 per

[131] Keiding and Tuller Diabetes, *4*, 37, 1955
[132] Turnblum and Nordstrum Acta Endocrinol , *17*, 426, 1954
[133] Engleson Acta Ped , *13*, (Supp 97), 132, 1954

atherosclerosis is limited Premarin (2.5 to 5.0 mg. per day) to correct [illegible]

weight are in progress

Estrogen therapy in diabetic males presents a different problem Feminizing side effects must be balanced carefully against the atherosclerosic potential in the individual

Although adrenal cortical hyperfunction is not definitely known to have a relationship to diabetic vascular disease, hormones elaborated by the adrenal cortex do have a potent effect on the mobilization of lipid from depots at the periphery. Such increased transport of fat may be more risky for the diabetic with vascular disease Therefore, efforts should be made to minimize dosage and duration of treatment with ACTH and steroids

Hypertension.—The harmful effects of persistent arterial hypertension in the diabetic have long been known As is generally true, systolic hypertension, especially in females, has proven less serious than elevation of diastolic pressure

[illegible]

produced by renal arteriolar disease (caused in part by diabetes) accelerates atherosclerosis

[illegible]

sion, similar measures may be applied, except when these patients are young diabetics of long duration with albuminuria and significant impairment of renal function In such patients heroic attempts to reduce diastolic hypertension may not be justified Since 1952 bilateral lumbodorsal sympathectomy and splanchnicectomy have been discontinued Surgical treatment of hypertension by lumbodorsal sympathectomy was used in a few carefully selected diabetic patients[158–160] when other methods of treatment failed to give relief from symptoms, or to halt malignant hypertension Except in the rare instances where antihypertensive agents do not control [illegible]

diabetic patients for two important reasons. (1) Severe, progressive or malignant hypertension is strikingly rare (2) The younger, longer-duration

[158] Smithwick Jour Med Soc New Jersey, 44, 301, 1947

[159] Hammerstrom Arterial Hypertension, In, Papers from 4th Med Service St Erik's Hospital, Stockholm, Sweden, p 219, 1948

[160] Evans and Bartels Ann Int. Med, 30, 307, 1949

about diabetes both to diabetic patients and to the public, will yield good results in the *prevention of these premature lesions*.

Special consideration of certain factors in relation to the prevention of atherosclerosis may be mentioned. Diet today is a subject of much discussion with relation to the fat intake. The restriction of dietary animal fat within limits is desirable, although it must be admitted that apparently, cholesterol levels in the blood serum although affected by intake, are in many instances resistant to control by diet alone. *In the diabetic patient, the lipids of the blood when elevated seem more rapidly affected by the intelligent use of insulin than by any other single factor.* In the presence of elevated serum cholesterol and lipid values, the diabetic diet may be altered by a reduction in fat content so that fat supplies only 25 to 30 per cent of the total calories. This may be accomplished by providing 2 grams of carbohydrate for each gram of fat removed from the diet and is more [illegible]

[illegible] fats omitted from the diet, has been adopted as a dietetic measure in a number of diabetic patients with high values for serum lipid and particularly in the presence of severe vascular lesions. In general, fats that are liquid at room temperature contain varying quantities of such unsaturated fatty acids. Soybean, corn and cottonseed oils contain about 50 per cent poly-unsaturated fatty acid by weight, chiefly as linoleic acid. By adding 30 grams, or 1 ounce of these twice a day, one would thus be including one-half this quantity as unsaturated fatty acid. For example, *if the case mentioned above under the first plan needed at least carbohydrate 150, protein 70 and fat 70 grams or more to maintain body weight, the fat from saturated sources could simply be reduced to about 20 grams per day and supplemented with 30 grams of corn oil twice daily. This would result in a diet containing carbohydrate 150, protein 70 and fat 70 to 75 grams (total).*

Many foods of marine and vegetable origin contain various amounts of poly-unsaturated fatty acids (See page 282).

Although one may wish to temporize for a while with an elevated cholesterol level that fails to respond to adequate control of diabetes and maintenance of ideal weight or the addition of moderate exercise, the diabetic is so prone to atherosclerosis that if he has a demonstrable atherosclerotic lesion, application of one of the above measures, or a reasonable variation, is clearly justified.

[illegible]

post-menopausal female and in the male indicate a genuine potential for [illegible] The combination of estrogen and [illegible]

given further trial, especially for the control of lesions in small vessels.

Our present experience with estrogen therapy for the prevention of

stant rather than intermittent, the loss of sodium and chloride may be marked over a period of time and thus make rigid salt restriction unnecessary Since loss of these ions may be unpredictable in quantity and the degree of responsiveness of the renal tubule may vary a great deal in diabetic patients with impairment of renal function, the diabetic should be observed at frequent intervals to determine the presence of electrolyte imbalance or depletion

E RENAL DISEASE

Introduction —A wide variety of renal complications occur in diabetic

ney or a transfusion reaction, urinary suppression due to sulfonamide administration or embolism have been observed at the New England Deaconess Hospital Certain reversible metabolic phenomena are associated with diabetic states Thus, glycogen deposition in the tubules occurs during marked glycosuria

frequently found in patients

of conditions commonly inc

quent It is the syndrome of diabetes albuminuria and hypertension

A. Diabetic Nephropathy
B Glomerulonephritis,
  1 Acute
  2 Chronic
C Arteriolar Nephrosclerosis
D Nephroses

more years duration with onset in childhood and youth The fact has come out that in diabetic patients both young and old

glomerulosclerosis rarely occurs a

ment is almost invariably of mix

tion and infectious elements It

12, 83 1936
116, 459, 1941
r Med, *3*, 131, 1947
Loc cit p 421
Med, *238*, 876, 908, 1948

diabetic developing hypertension is frequently so ill with renal disease, that rigid adherence to a diet containing 450 grams of carbohydrate, about 22 grams of vegetable protein, about 3 grams of vegetable fat and less than 50 mg. of sodium per day is intolerable. However, one patient (Case 37799) aged 54 years, cooperated intelligently in adhering to a modified rice-fruit diet for over a year. Blood pressure was reduced from 220 systolic and 124 diastolic to levels of 146 to 156 systolic and 90 diastolic. Nitrogen balance was maintained on the modified rice diet and the weight remained constant. In several younger patients, edema has been controlled, blood pressure lowered, and insulin dosage also lowered. However, in the younger group where renal disease has progressed, there has been no evidence to show this treatment has altered the eventual fatal outcome.

Studies of the rice-fruit diet indicate that fall in blood pressure is related to loss of sodium and water with consequent reduction in extra-cellular fluid. Chapman and Gibbons[142] found definite lowering of blood pressure in 8 men with moderately severe essential hypertension, but the blood pressure resumed pre-treatment levels when salt was added to the diet. Moderate sodium restriction, in conjunction with attempts to bring weight down to normal levels, is frequently used in diabetic patients with hypertension, but in the absence of edema such restriction rarely goes below 1 gram of sodium per day. With the recent addition of chlorothiazide to the antihypertensive armamentarium, salt intake has been liberalized to varying degrees.

Antihypertensive Agents.—Treatment of our diabetic patients with hypertension, particularly when diastolic levels exceed 100 mm. Hg, has run the gamut of the newer agents appearing in the last seven or eight years. No clear-cut data concerning the results of treatment with most of these are available, but rauwolfia alkaloids have been sufficiently effective in the patients with labile hypertension that they have been used frequently, occasionally with dramatic results. A few patients have done well when hydrazaline (apresoline), 25 to 50 mg. four times a day, has been added to the rauwolfia therapy.

Recently chlorothiazide[143,144] (Diuril) has created sufficient interest that a study is now underway to evaluate carefully its effect in our diabetic patients. It produces diuresis by a profound excretion of sodium and chloride, and to a lesser degree of potassium and bicarbonate.[145] Lowering of blood pressure occurs as a result of diuresis and an as yet unexplained additional antihypertensive action,[146] which appears to be enhanced by the prior or simultaneous administration of rauwolfia in therapeutic doses. Chlorothiazide has been particularly active when the glomerular filtration rate is not grossly impaired.[147]

Potassium loss may be marked and necessitate administration of potassium salts by mouth. Furthermore, since the effect on the tubule is con-

[141] Kempner. Amer. Jour. Med., *4*, 545, 1948.
[142] Chapman and Gibbons. Medicine, *29*, 29, 1950.
[143] Wilkins. New England Jour. Med., *257*, 1026, 1957.
[144] Fries *et al.* Ann. New York Acad. Sci., *71*, 450, 1958.
[145] Beyer. Ibid., 363, 1958.
[146] Wilkins, Hollander and Chobanian. Ibid., 465, 1958.
[147] Shreiner. Ibid., 420, 1958.

child leaves home for work or for school or college urine tests become infrequent and doctors' visits rare. Episodes of diabetic acidosis or coma may occur with recovery. After ten or fifteen years of such treatment the patient, now in his late twenties, begins to show proteinuria. Examination reveals intermittent proteinuria, but associated increase in the capillary fragility index and occasional punctate hemorrhages or micro-aneurysms are seen in the periphery of the retina Within two years other signs and symptoms appear. Proteinuria has become constant and peripheral edema is present at times. Microscopic examination of the sediment will show doubly refractile fatty cells and casts in the urine at times. Red blood cells are few or absent. Periods of acute pyelonephritis with fever may occur Hypertensive levels occur. Calcification is found within the arteries of the legs or pelvis by roentgenography Despite attempts to control the diabetes severe kidney damage has been established Renal insufficiency progresses with massive proteinuria leading eventually to hypoproteinuria, anemia and finally constant azotemia. The terminal weeks or months are charac-

Dana,[161] has frequently occurred in our experience and in the series of Epstein and Zupa [162]

Diagnosis may be made on finding marked albuminuria, nephrotic edema, hypertension and diabetic retinopathy. The latter frequently precedes albuminuria and edema, but is always present when other findings have appeared Diagnosis is more assured in the presence of long duration of diabetes with onset early in life The condition is rare in diabetes of less than 10 years duration and more frequent after 12 years [16?] In older patients with asymptomatic diabetes, the duration of diabetes may erroneously be recorded as "short" ...

ing

making the diagnosis However, such lipid material may occur in other conditions (Lippmann) [164] Elevation of the serum cholesterol or lipoprotein level is also indicative (Keiding, Mann, Root, Lowry, and Marble) [165] Addis counts may help in that hematuria suggests glomerulonephritis since it is rarely found in diabetic nephropathy

Incidence of this condition appears variable due to the fact that in older diabetic patients the nephrotic features are frequently much less marked than is true in younger people Autopsy reports frequently include only older patients, with but an occasional examination of patients under 30 years of age Even when a few young patients have been included usually they were patients dying of diabetic coma after only two or three years of

Med, 245, 518, 1951

149

ed Springfield, Ill, Thomas,

p

[165] Keiding, et al Loc cit p 420

28

acute and chronic pyelonephritis, *intercapillary glomerulosclerosis and* arteriosclerosis which is seen with the greatest frequency and to which it [illegible]

portion of the glomerular lobule, and (2) the diffuse types in which strands of hyaline material extend into the intercapillary spaces. The globular masses are considered *pathognomonic of diabetes. The diffuse type is less* specific (see page 183), appears to precede and may be more important functionally.[153]

In recent years, a type of lesion, which was described by Kimmelstiel and Wilson but not emphasized by them, has been called the "exudative lesion" by British workers[154, 155] and also has been described by Koss and Barrie[156, 157] *et al.* It consists of a mass of homogeneous "fibrinoid" material, differing in texture, color and location from the classical hyaline nodular lesion of Kimmelstiel and Wilson. This exudative lesion can be distinguished in the electron microscope by its density as well as its location.[158] It is usually a late or terminal phenomenon in diabetic nephropathy, and clearly not [illegible] be found in other diseases,

when, for example, it is said that the lesions "resemble those of human [illegible]betic glomerulosclerosis," whereas the lesions induced by these steroids are clearly of the non-specific exudative type.[160]

The hyaline deposits in the glomeruli resemble amyloid, but most authors *agree that it cannot be so identified. The use of the periodic acid stain,* however, strongly suggests that this material and the hyaline material in retinal arterioles, islands of Langerhans and basement membranes seen in diabetic patients are related. It is this feature which unifies present concepts of diabetic pathology. So far it appears that the complete clinical syndrome with edema of the nephrotic type, albuminuria, hypertension and diabetes occurs in a relatively small percentage of the patients who have a *pathologic picture of intercapillary glomerulosclerosis.* However, it can be said that diabetes occurs in almost all cases of intercapillary glomerulo-

the cardinal symptoms of diabetes within a few weeks. The condition is brought under control with diet and insulin treatment. During the next few years the child and the parents are instructed and carefully follow directions so that the diabetes is well controlled. Gradually the management of the child's condition becomes less careful and particularly as the

[153] Gellman *et al.* Presented at Annual Meeting of A. M. A., San Francisco, June 21, 1958.
[154] Hall. Jour. Path. and Bact., *64*, 103, 1952.
[155] Anderson. Ibid., *67*, 241, 1954.
[156] Koss. Arch. Path., *54*, 528, 1952.
[157] Barrie, Aszkanazy and Smith. Canad. Med. Assn. Jour., *66*, 428, 1953.
[158] *Farquhar, Hopper and Moon. Jour. Exper. Med., (in press).*
[159] LeCompte. Loc. cit. p. 409.
[160] LeCompte. Diabetes, (Editorial), *7*, 495, 1958.

lesions of diabetic nephropathy may be postponed or prevented (Wilson, Root, and Marble, see page 409).

B Glomerulonephritis.—In its acute form, glomerulonephritis probably occurs in diabetic patients with about the same frequency as in non-diabetics of the same age Thus Case 21087, with diabetes of six years' duration, developed at the age of thirty-one years, acute glomerulonephritis with an elevation of blood pressure, bilateral choked discs, and almost complete blindness from which he made an excellent recovery in June, 1944. He had been well, with freedom from albuminuria, normal blood pressure and nor-

The occurrence of gross hematuria with facial edema after an acute upper respiratory infection supports the diagnosis In Case 13433, male, age 16 at onset of diabetes in 1933, the diabetic nephrophathy was well established by 1945 Two years later gross hematuria and facial edema developed The acute nephritis continued for three weeks with final complete clearing

hyalinized Most of the glomeruli contained pink-staining areas characteristic of intercapillary glomerulosclerosis

Chronic glomerulonephritis has occurred no more frequently in diabetic than in non-diabetic patients In spite of the diabetic susceptibility to

Gruber and Spuhler [174]

Clinical Course —The various classical manifestations of hypertension characterize the course, including headache, nervousness, sleeplessness and

[169] LeCompte Loc, cit, p 409
[170] Bell Loc, cit, p 408
[171] Moschcowitz Vascular Sclerosis, New York, Oxford Univ Press, 1942, Ann. Int. Med 34 1137 1951
[172] Warren and LeCompte Pathology of Diabetes, 4th Ed in press
[173] Tobler Schweiz Med Wchnschr, 43, 1213, 1934
[174] Gruber and Spuhler Zur Physiopathologie der Niere, 1946.

diabetes before this condition developed. Lambie and MacFarlane's[166] study of 120 post-mortem examinations of diabetics, included only 7 patients under 40 years of age, and 80 in their series were between 60 and 80 years of age. Both nodular and diffuse types of glomerulosclerosis were found in older diabetic patients without clinical diagnosis. Prolonged duration of diabetes, and imperfect control were marked features in the patient showing the lesions in contrast with those diabetics without the lesions. In a group of 247 long-standing diabetics the young patients submitted to careful x-ray study of peripheral arteries and evaluation of the kidneys, 63, or 35 per cent were found to have diabetic nephropathy by Wilson, Root and Marble.[167] In a follow-up of 847 diabetic patients with retinitis proliferans, uremia due to diabetic nephropathy was the cause of death in 147 out of 331 deaths. In a series of 153 diabetics with the triopathy (neuropathy, retinopathy, nephropathy), uremia was the cause of death in 33 of 51 cases, and was the cause of death in 18 of the 23 deaths in which post-mortem examination was done (Root, Pote, and Frehner)[168] Diabetic nephropathy now takes first place as the cause of death in youthful patients after 14 years or more of diabetes.

AIDS IN TREATMENT OF NEPHRITIS IN YOUNG DIABETICS OF LONG DURATION

Treatment will vary with the stage of the disorder. Mecurial diuretics may be employed. The following schedule will serve as an aid in selecting treatment in the nephrotic, page 431, or uremic stage, page 435

The nephritis (diabetic nephropathy) is commonly first indicated by recurring edema. Then, or later, appear persistent albuminuria and in many cases an increase in the plasma lipids (nephrotic phase). Later manifestations include hypertension, increased albuminuria, cylindruria, cardiac failure and uremia. Insulin need may decline.

[illegible] at any stage. In the female, [illegible] If infection [illegible] may be tried [illegible] be utilized

If clinical symptoms exist, with few white cells in urinary sediment, a colony *count exceeding 100,000 colonies cc* usually indicates active infection. If bacteria are seen on stained smear of sediment, colony count is usually [illegible]

[illegible] condition developing in the severe diabetes of childhood shows it to be directly related not only to the duration, but to the severity of the diabetes. It must be granted that we cannot define the severity of diabetes since insulin dosage is notoriously unreliable in this respect. Evidence accumulating from the records of patients long under good control, show that the

[166] Lambie and MacFarlane Quart Jour Med, 24, 125, 1955
[167] Wilson, Root, and Marble Loc, cit, p 400
[168] Root, Pote and Frehner Arch Int Med, 94, 931, 1954

UREMIC STAGE

Clinical

Nitrogen retention (nonprotein nitrogen 45 mg. to 100 mg. per 100 cc. or higher). Hypertension (usual), albuminuria, cylindruria, retinopathy Edema variable Refractory anemia without reticulocytosis frequent

Diet

1 Salt-free diet (except when low chloride syndrome threatens) Avoid potassium

2 Protein 0 5 to 1 0 grams per kilogram body weight, or as little protein as is compatible with nitrogen equilibrium (40 to 60 grams protein per day.)

3 Liquids unrestricted, except in presence of oliguria

4 If anuric or oliguric (200 cc urine or less per day)

Total water/24 hours=800 cc plus measured loss of fluid

I V —Dextrose 100–300 gms in the allowed amount of water (20–50 per cent solutions)

Oral—Karo syrup and ginger ale (25 cc of each) per hour gives many calories in desired amount of water over a 10–12 hour period

Fat (such as butter) may be needed to offset protein catabolism

Daily weight mandatory to check net fluid balance

Drugs

1 Alkalies (sodium lactate) if nephritic acidosis with low plasma CO_2 is present

2. Colloidal aluminum hydroxide 8 cc. 4 times a day in chronic uremia to prevent phosphate absorption Aluminum carbonate (basolgel) more effective

For Cardiac Insufficiency

1 Bed rest

2 Fluid at 2000 cc per 24 hours if oliguria present

3 Digitalis

For Anemia

Transfusion with packed red blood cells (whole blood if necessary) *only if* weakness attributable to severe anemia is present

For Acute Encephalopathy

1 Magnesium sulphate 2 cc 50% solution I M , P.R N

2 Hypotensive drugs, Reserpine I M , or ganglionic blockers

For ECG Changes

Rising serum K+ is ominous, if peaked T waves and flattened P waves appear Withhold protein and fruit juices (exogenous K)

characteristic of glomerulonephritis than of nephrosclerosis but is found frequently in the latter condition. Cardiac hypertrophy with dyspnea and congestive heart failure frequently occur The degree of cardiac enlargement seems greater when hypertension has long preceded the onset of diabetes than in cases where hypertension and coronary sclerosis have followed long after the onset of diabetes

Differential Diagnosis.—Nephrosis with depression of serum protein and inversion of the albumin-globulin ratio does not occur in arteriolar nephrosclerosis, as it does so frequently in the Kimmelstiel-Wilson syndrome

of glomerular nephritis, although papilledema may be more frequent The occurrence of renal types of hemorrhage and exudate in contrast to the

NEPHROTIC STAGE

Clinical:

Albuminuria, edema, normal nonprotein nitrogen (40 mg. per 100 cc or lower) low serum protein, increased serum lipids (cholesterol may be 250 to 1000 mg per 100 cc). Retinopathy present.

Diet:

1 Salt-poor (less than 1 gram sodium daily) except in salt-losing phases, or if on Chlorothiazide. Salt substitutes may be used.

2. Acid-ash (but not at expense of sodium restriction) To obtain an acid-ash diet, milk, fruit and certain vegetables, which are basic, must be restricted The acid forming foods include meats, eggs, fish, bread and cereals.

3 Moderate protein (50 to 100 grams daily) even if hypoproteinemia is present

4 Liquids unrestricted usually.

5 If cholesterol markedly elevated, consider reduction of dietary fat to 25 per cent of total calories and substitution of unsaturated fatty acids (vegetable fats) in part

Drugs

A Diuretics

1 Ammonium Chloride (4-8 grams) 3 days on and off

2 Acetozoleamide (Diamox) 250 mg every 1 to 2 days

3 Chlorothiazide (Diuril) 500 to 1000 mg daily accompanied by potassium replacement 1-3 gms daily

4. Mercurials:

a. Meralluride sodium (mercuhydrin)—1-2 cc I.M.

b Mercurophylline sodium (mercuzanthin) 1-2 cc. I M.

c. Mercaptomerin sodium (Thiomerin sodium (Thiomerin)—1-2 cc. I M or S C

d. Chlormeradrin (Neohydrin) 18.3 mg tablets—1 to 4 tablets orally per day.

e. Mercuzanthin tablets containing *100 mg may also be used 1 to 2 per* day orally.

Mercurials not to be given I V. Oral preparations are to maintain relatively edema-free state, *not* to initiate treatment when edema well-established.

Aminophylline 250-500 mg. I V. after I M mercurial may occasionally effect diuresis when mercurial alone is ineffective, but this applies chiefly when cardiac failure with lowered glomerular filtration rate is a factor.

B Digitalis if heart failure is present or imminent

C Bed rest may rapidly effect diuresis

Special Measures in Selected Cases

1 Salt-poor concentrated human albumin (25-50 grams protein per day)

2 Cortisone, Prednisone or Triamcinolone *may be tried for 10-14 days* with a subsequent course of plasma expander (dextran) *for refractory cases*

palpitation. Instances of acute hypertensive encephalopathy are not rare Hypertension, frequently diastolic, may continue for years without any significant *abnormality in the urine Then proteinuria and casts may ap*pear If the disease is of a "benign" type, renal function may not be seriously reduced for yea[illegible] the picture of advancing nephritis may [illegible] the majority of patients, [illegible] or to failing glomerular function As edema accumulates rapidly, often the *insulin requirement rises When edema of either renal or cardiac origin* becomes chronic, the insulin dosage may fall rapidly to low levels or even to zero. Indeed it has been stated that with advancing vascular nephritis, mild diabetes may disappear. On the other hand, during the stage of azotemia, excessive hyperglycemia (500–1000 mgs. per 100 cc) has been seen in the absence of any ketosis Hematuria, gross or microscopic, is more

diac disease is the first cause of death among all diabetic patients with onset

Dextrocardia with complete situs inversus has occurred in two patients. Patent interventricular septum as well as cases of patent foramen ovale have been recorded, notably in one recent case where multiple emboli from the legs found loci in the brain through such a patent foramen ovale. Rheumatic valvular disease is infrequent, and infections such as syphilitic aortitis so rare that not more than three cases are recorded and other rarities, such as hemochromatosis, of the heart may only be mentioned.

Pathologic Physiology.—Heart muscle shows chemical changes during activity similar to those occurring in skeletal muscle with certain basic differences. Glycogen is present in considerable amounts but is relatively fixed and mobilized only in extreme anoxia and after the action of epinephrine. The glycogen can be reformed from glucose but not from lactate. Diabetic heart muscle shows an increase in glycogen content and starvation

ketone bodies derived from fat may account for almost 80 per cent of oxygen utilization. Fat and possibly certain amino acids are well utilized. Indeed, the heart can derive its sole energy from non-carbohydrate materials when necessary. Insulin does increase the utilization of glucose by the diabetic heart, an observation in keeping with the conception that basic pathways in carbohydrate metabolism are identical in cardiac and skeletal muscles.

Using coronary sinus catheterization technique, it has been demonstrated that normally (1) human myocardium utilizes fatty acids, which may account for as much as 34 per cent of the O_2 consumption of the heart,[176–178] (2) lactate and pyruvate, as well as glucose, are utilized maximally at arterial bloo ... high output in ... anical work the ... non-essential fatty acid (NEFA) by heart muscle is of sufficient magnitude to account for all the oxygen consumed.[179]

to ...

ar ...

does its share in their usage.[180]

[176] Bing et al. Am. Jour. Med., 16, 504, 1954.
[177] Bing et al. Ibid., 15, 284, 1953.
[178] Goodale and Hackel. Circulation Res., 1, 509, 1953.
[179] Gordon and Cherkes. Jour. Clin. Invest., 36, 810, 1957.
[180] Ungar, et al. Am. Jour. Med., 18, 385, 1955.

usual diabetic picture may help. Depression of renal function, including failing excretion of phenolsulphonthalein, retention of nitrogen and uremia are terminal events.

Treatment.—Control of diabetes in its earliest stages is of basic importance. Later, therapy resolves itself into the treatment of hypertension and of renal failure. A diabetic diet, which provides for carbohydrate 175 [illegible]

required to control high blood sugar levels than would be true in a patient without renal disease. The use of salt-poor diets, such as the Rice diet of Kempner, may reduce blood pressure and the serum cholesterol level but [illegible] The use of newer

[illegible] rare in our *experience at the New England Deaconess Hospital.* However, a nephrotic phase in the early stages of the diabetic nephropathy is of frequent occurrence in young diabetic patients of long duration. The pathologic lesion frequently found in nephrosis consists of abnormalities in the glomerular basement membrane. Thanks to Dr. Arnold Relman attention has been called to the occurrence of such a membranous glomerulonephritis in some diabetic patients. In two of our young cases renal biopsy demonstrated such a state. In one, a young male, improvement in his edema occurred without treatment with cortisone. The second, Case 50297, age 20, came *because of persistent edema. Diabetes began at the age of five years.* Her control had been good during the first few years, but since the age of 12, glycosuria had not been controlled. Edema was accompanied by slightly lowered serum protein value, and an elevation of the serum cholesterol to 353 mg. The biopsy showed some definite thickening in the basement membrane, and early arteriolarsclerosis. Treatment with cortisone in high dosage has been begun. After three months (January, 1958) her condition shows improvement in that edema is absent. Her weight which at one time reached 138 pounds is now 117 pounds. Judgment as to her future course *must be reserved with caution particularly in view of the difficulty of* interpreting biopsy results until further experience is available. In the series of 12 cases with renal biopsy findings reported by Brun, *et al.*[173] six showed only diffuse glomerular changes. In 4 cases nodular-diffuse changes where present, and in one case completely hyalinized glomeruli were found. If it be true that diabetic nephropathy originates as diffuse hyalinization in the basal membranes of the glomerular tufts and the nodular changes may be considered a further development then the later course in the patient described may be that of the typical diabetic nephropathy.

F. HEART DISEASE AND DIABETES

Whereas the diabetic nephropathy has become the chief cause of death among diabetic patients with onset of diabetes in childhood or youth, car-

173 Brun, Gormsen, Hilsen, Iversen and Rasschou. Am. Jour. Med., *15*, 187, 1953.

(*b*) The clinical and electrocardiographic disturbances of hyperkalemia are of importance in the diabetic. The accumulation of toxic amounts of potassium may occur by reason of excess intake, increased cellular breakdown as in severe ketoacidosis, and decreased excretion by failing kidneys (the critical factor in diabetic patients)

Although early recognition of renal failure and the avoidance of potassium intake are important measures in reducing the severity of clinical manifestations of hyperkalemia, success or failure will depend on reversibility of renal failure to the point where potassium excretion can occur The frequency of nephropathy in young diabetic patients has made us hesitate to advocate the routine administration of potassium salts but rather to depend upon the combination of electrocardiograms and blood measurements as guides to treatment.

Symptoms include listlessness and mental confusion, numbness and tingling of the extremities, cold, gray pallor, bradycardia, peripheral vascular collapse, and in a few patients with uremia,[193 194] rapidly ascending flaccid paralysis and cardiac arrest Paralysis accompanying hyperpotassemia has recently been re-emphasized [195]

As with depleted potassium vital information may be gleaned from the electrocardiogram before serum potassium can be measured

In the case reported by Root, Story and Cortese,[196] symptoms were slight but the changes in the electrocardiogram were extreme with a potassium value of only 8 2 milliequivalents

Although abrupt potassium accumulation may produce cardiac effects with electrocardiographic changes when the absolute level of serum potassium is only moderately elevated while gradual development of hyperkalemia may be well-tolerated, the eletrocardiographic changes do correspond in crude fashion to the degree of serum potassium elevation, according to Darrow [197] At concentrations of 6 5 to 7 8 millimols of potassium per liter alterations in the T-waves begin to appear and are almost constantly present when the potassium level is above 8 millimols per liter Heart block appears when potassium is about 10 millimols per liter

Chemical changes of hyperkalemia may be unassociated with the clinical symptoms [198] In the second of their 9 cases the changes most marked in the patient occurred when the serum level was 9 5 mEq 1 , and yet a fall of only 0 4 mEq 1 was accompanied by a most striking improvement in the appearance of the tall, pointed T-waves of the electrocardiogram In four patients whose potassium levels were elevated from 8 3 to 8 8 mEq 1 per liter, 2 with depressed sodium levels showed quite marked electrocardiographic changes, whereas the other 2 patients with normal serum sodium levels showed little electrocardiographic evidence of potassium poisoning

Typical changes appearing in sequence are (1) appearance of peaked T-waves, (2) increased duration of the Q-R-S complexes, (3) increased duration of the P-R interval leading to auricular stand-still, (4) biphasic

[193] Kolff Jour Lab and Clin Med 36 71 1950
[194] Ball Carter and Lowe Lancet, 2 60 1953
[195] Gunstorp *et al* Am Jour Med, 21 185, 1957
[196] Root Story and Cortese New England Jour Med 245 765 1951
[197] Darrow and Pratt Jour Am Med Assn, 154, 432, 1950
[198] Merrill *et al* Ann Int Med, 33, 797, 1950

Following insulin, the diabetic heart shows a net increase in glucose, [illegible]

O_2 consumption.

During recent years the effects of disturbances in potassium and sodium concentrations in the blood upon cardiac function during diabetic coma, shock, uremia and lower nephron nephrosis have been reported frequently.[187-190]

(a) Low concentrations of potassium in blood serum are accompanied by certain symptoms, physical signs and electrocardiographic changes. The following have been observed: (1) a weakness of the skeletal muscles progressing to frank paralysis, (2) dyspnea with a shallow gasping type of respiration in which the accessory muscles of respiration are involved (3) cyanosis, (4) abdominal distention, (5) nausea and vomiting, (6) cardiac enlargement, (7) increased pulse pressure with a Corrigan pulse, (8) elevated venous pressure and signs of cardiac failure. The electrocardiographic changes accompanying low concentrations of potassium include (1) slightly prolonged Q-T interval, (2) decreased height and the inversion of the T-waves, (3) rounded and prolonged T-waves, (4) depression of the S-T segments, *and (5) prolonged P-R interval, inversion of the P waves* and extra systoles The precordial lead CR_4 has been found most useful in measuring the Q-T interval. Since it is impossible to predict how often and under what circumstances low concentrations of potassium in the serum lead to anatomic lesions in the heart or when serious symptoms may develop, low potassium values must be suspected under conditions where an excessive loss of potassium from the body or deficient intake as in the nausea and vomiting of diabetic coma have occurred. The use of the flame photometer makes possible rapid estimation of blood values and during the last few years observations upon the sodium and potassium of the blood in our diabetic coma patients together with electrocardiograms have been frequent The popularity of the electrocardiogram in the diagnosis of significant potassium deficiency continues because it is easier to obtain and it indicates earlier and more accurately the intracellular concentration of potassium On the other hand, Schwartz, Levine, and Relman[191] found no consistent relation between the electrocardiogram or the serum potassium [illegible] "moderate." [illegible]

TABLE 79.—CORONARY OCCLUSION IN DIABETIC AND NON-DIABETIC PATIENTS IN PERCENTAGE OF CASES IN AGE GROUPS

Age Groups	Males				Females			
	Diabetic		Non-diabetic		Diabetic		Non-diabetic	
	Cases with Occlusion	Per Cent of Total	Cases with Occlusion	Per Cent of Total	Cases with Occlusion	Per Cent of Total	Cases with Occlusion	Per Cent of Total
41–50	2	15	23	7	3	11	2	1
51–60	13	33	47	10	13	25	8	3
61–70	28	48	52	11	26	40	17	7
71–80	9	41	24	11	13	43	9	10

curves with progressive delay of ventricular conduction and (5) standstill. Changes may begin when serum potassium is 5.5 mEq/l. or higher.

Coronary Atherosclerosis.—Coronary arteriosclerosis is seen at least twice as frequently in diabetics past 40 years of age with hypertension as *in diabetics of similar age without hypertension. The influence of genic* factors may be important, for it is observed that in diabetic patients followed for periods of 10 to 20 years the incidence of diabetics among their relatives rises steadily to 40 or even 50 per cent.

(*a*) *Angina Pectoris.*—In the past the experience with diabetic patients suffering from angina pectoris has been much less favorable than in comparable series of non-diabetic patients. Root and Sharkey[199] noted that [illegible]

[illegible] iset [illegible] oot [illegible] per cent of non-diabetic subjects reported by White[200] survived the first year. Today the experience with diabetic patients is certainly much improved, especially if he can survive the first year, make adjustments to his condition, *and particularly if the development of intercoronary anastomases occurs.* The angina of the diabetic is predominantly that of exertion. Where the diagnosis is questionable, the "two-step exercise test" as standardized by Master[201] has been used. It is of value as a diagnostic aid and rarely has the "double" test been necessary. Atypical forms of angina pectoris are *frequent in diabetic patients, in whom the localization of pain may be in* the neck, in the back or in the abdomen with surprising frequency. Treatment is greatly aided by early diagnosis. Symptomatic relief is usually obtained by nitroglycerine. Peritrate and other long-acting vasodilator [illegible]

[illegible] sized. Surgical methods and thyroid ablation have been employed rarely.

(*b*) *Coronary Insufficiency.*—The condition of coronary failure somewhere between angina pectoris and infarction has long been recognized. Chest pain with severity and duration resembling infarction but without shock, heart failure, or friction rub, and with only ischemic changes in the ECG, and diagnosis [illegible]

[illegible] frequently there may be congestive failure requiring the usual methods for its management.

(*c*) *Myocardial Infarction.*—It is not only characterized by the great frequency of this condition as a cause of death in diabetics but particularly the fact that female diabetics have almost an equal incidence with the male

199 Root and Sharkey. Ann. Int. Med., 9, 873, 1936.
200 White *et al.* Jour. Am. Med. Assn., *123*, 801, 1943; Heart Disease, 4th ed., New York, Macmillan, 1951.
201 Master *et al.* New York State Jo[illegible]

Difficulties arise from the
nts have frequently ab-
arction may make little
changes are difficult to
interpret

TABLE 80 —DURATION OF SURVIVAL FOR 102 DIABETICS FOLLOWING ACUTE MYOCARDIAL INFARCTION (1913 TO 1918, INCLUSIVE)[203]

Survival Attained	*Survivors* No	*Survivors* Per cent	*Living at end of Survey**	*Incomplete Follow-up*
Less than 60 days	62	60.8	0	–
60 days to less than 1 yr	40	39.2	0	1
1 yr	31	30.4	0	–
2 yr	27	26.5	0	–
3 yr	21	20.6	0	1
4 yr	17	16.7	0	–
5 yr	16	15.7	1	1
6 yr	11	10.8	4	–
7 yr	7	6.9	0	–
9 yr	6	5.9	1	–
10 yr	3	2.9	0	–
11 yr	1	1.0	0	–
12 yr	0	0	0	–
First Infarctions Only				
Less than 60 days	48	57.8	0	–
60 days to 1 yr	35	42.2	0	1
1 yr	27	32.5	0	
3 yr	20	24.1	0	1
5 yr	16	19.3	1	1
10 yr	3	3.6	0	–

* Reports or examinations during 1954, February through October

Regular use of serum glutamic oxaloacetic transaminase activity (SGO-T) in the p[illegible]
abnorm[illegible]
ficult
insuffici[illegible]

Since the enzyme is present in large amounts in heart muscle, skeletal muscle, brain, liver, and kidney, injury to these tissues results in release of enzyme into the circulation Their level of normal in human sera equals 15 to 40 units An upper limit of 40 units has been accepted at the New England Deaconess Hospital Since elevated serum levels in myocardial infarction occur 9 hours after the attack and are already approaching normal 3 days later, blood should be drawn soon after the attack and at

[203] LaDue, Wroblewski and Nydick Mod Concepts of Cardiovas Dis, 24, 333, 1956

A comparison of diabetic and non-diabetic autopsies by age and sex has been summarized by Root, Bland, Gordon and White.[202] (Table 79).

The reversal of the sex ratio in coronary disease among diabetics has been confirmed repeatedly.[203, 204]

The prognosis for diabetic patients with myocardial infarction has been much worse than in non-diabetics of similar age, especially in the first attack and when accompanied by diabetic decompensation. *The mortality for acute episodes at the New England Deaconess Hospital among diabetics persisted through the year 1953 at 60 to 62 per cent, but it has lessened slightly in 1958 to just under 50 per cent. Whether this is related to the more consistent use of anticoagulants is, as yet, uncertain.*

The late survival of diabetics who live beyond the first two months is almost as good in the diabetic as in the non-diabetic in the experience of Katz, Mills and Cisneros.[205] *Experience with diabetics admitted to the New England Deaconess Hospital has been less favorable. Table 80 shows the total 102 diabetic subjects, 30.4 per cent of whom survived for one year, 20.6 per cent for three years and 15.7 per cent for five years after onset of acute myocardial infarction. About 5 per cent of the series die each year from the end of the first through the fifth year. The six survivors at the end of the survey in 1954 were alive almost four years later. It should be further noted that survival beyond ten years is unusual.* Rehabilitation and a more favorable prognosis after infarction have been stressed repeatedly. Apparently the diabetic suffers less by comparison with the non-diabetic once he has recovered from the first acute infarction.[206] Diabetics can fare well for a great many years with continuous good treatment. Root and Barclay[207] found 96 patients with diabetes for 35 to 46 years, *51 of whom were living in 1955 at ages 43 to 85. Although all 46* fatal cases died of coronary heart disease, such a series of long-lived patients is encouraging to doctor and patient alike.

Clinical problems are presented when myocardial infarction and diabetic ketosis occur together with shock and dyspnea. The prognosis is much [illegible] appears when

remembered when a diabetic patient behaves differently with respect to the abrupt onset of hyperglycemia and increased glycosuria, or unexplained hypotension, or an arrhythmia, especially auricular fibrillation, with or without the associated symptoms, unexplained edema or weight gain; and, of greatest importance, the occurrence of otherwise unexplained congestive failure.

"Silent" infarction is really rare, if silence means the absence of any pain. Infarction without alarming pain, however, is not infrequent. The electro-

[202] Root, Bland, Gordon and White. Jour. Am. Med. Assn., *113*, 27, 1939.
[203] Bradley and Bryfogle. Am. Jour. Med., *20*, 207, 1956.
[204] Thomas, Lee and Rohan. Arch. Int. Med., 98, 489, 1956.
[205] Katz *et al.* Loc. cit., p. 411.
[206] Bradley and Bryfogle. Loc. cit., p. 442.
[207] Root and Barclay. Jour. Am. Med. Assn., *161*, 801, 1956.

thrombophlebitis The use of elastic stockings is not indicated, since ace bandages are preferred At present most of our diabetic patients with a serious infarction receive Heparin (usually aqueous) 50 to 75 mg every 6 hours for the first 24 to 72 hours until dicumarol has sufficiently lowered prothrombin activity. Thereafter, dicumarol, tromexan, hedulin, or sintrom are continued alone Prothrombin activity is kept between 10 and 30 per cent.

Congestive heart failure is extremely common among middle-aged and elderly diabetics with long-standing coronary arteriosclerosis or infarction [illegible]

[illegible]

last ten years Epinephrine, ephedrine, isopropylarterenol, and recently the electric external pacemaker have been used with varying degrees of success or failure [212] One woman, case 29852, in particular illustrates the use of an array of agents and the "Pacemaker." At age 74, with diabetes of 12 years duration and the systolic murmur of aortic stenosis present for at least 7 years, she developed increasingly frequent "black-outs" over a three-month period ECG during attacks showed abrupt idioventricular rhythm at 40 per minute Ephedrine and isuprel in combination usually maintained sinus rhythm at 75 to 80 per minute, but at times the "Pacemaker" was required Death occurred 6½ months later in attack

Ability to survive with or following Stokes-Adams attacks, whether based on ventricular standstill, idioventricular rhythm, or ventricular fibrillation will depend on the degree of injury and or ischemia of the myocardium produced by the underlying disease.

Associated complications include first of all diabetic nephropathy. Decreased glomerular filtration as a result of congestive failure is frequent Therefore, close observation of urine output and caution in the administra- [illegible]

Control of Diabetes—Severely uncontrolled diabetes is a frequent accompanying feature of acute myocardial infarction Coma, or acidosis without ketosis occurring on occasion, presents an extremely serious prognostic sign The evidence indicates that failure to treat diabetes adequately may well have a harmful effect on the myocardium, and the serious defects in intracellular metabolism as a whole are well-established. Ignoring the metabolic turmoil of uncontrolled diabetes is *not* justified by the attitude that hypoglycemia must be avoided "at all costs" to prevent the effects of epinephrine on the heart

[212] *Zoll et al* Arch Int Med, 96, 639, 1955

least one other specimen taken a day later for confirmation and to be certain a level at or near the peak rise is obtained. SGO-T activity may also give a reliable gross estimate as to size of the infarcted area.[289]

Treatment.—Individualization of treatment in the diabetic is necessary. The "armchair" treatment, recommended by Levine, has been used in a few diabetic patients with great emphasis upon the precautions which he has described so carefully. Lifting and feeding the patient are stressed. The harmful effects of prolonged bed rest are circumvented by the following: (1) all diabetic patients with acute episodes have blocks 6 to 9 inches in height placed under the head of the bed. Recent use of adjustable beds which allow the feet to be lowered and the head to be raised to a 9- or 10-inch elevation of the head above the horizontal; (2) bed rest may be maintained for a limited number of days before the institution of arm-chair treatment, (3) the use of a bedside commode The critical condition of most diabetic patients with acute myocardial infarction has made us extremely hesitant to adopt chair treatment in many instances Hospital beds can be lowered to near the floor level and allow us to "roll" patients from bed to chair and back again

Shock, when profound and persistent, is a sign of grave significance. Earlier use of Neosynephrine 5 to 10 mg., methoxamine (Vasoxyl) 20 mg., [illegible]

effects of Levophed on the blood pressure can be carefully titrated except when little or no response occurs, usually indicating early terminus. Volume of fluid can be curtailed by using larger amounts of Levophed per unit of solution Potent peripheral vasoconstrictor action of arterenol (norepinephrine) makes it extremely hazardous in the lower extremities of the diabetic. Never should Levophed be given in any vessel at knee-level or below A "cutdown" on an arm vein is almost always preferable. Plasma, dextran, blood by vein or intra-arterially are not used except when significant loss has occurred, as in gastro-intestinal hemorrhage [illegible]

Anticoagulants.—Since the repo [illegible] role of dicumarol in reducing mor [illegible] it has been used cautiously at the [illegible] opinion has gradually swung in [illegible] according to a prognostic category as suggested by Russek and associates.[291] Anticoagulants were indicated especially for the "poor risk" group who were described as (1) patients with previous myocardial infarction, (2) intractable pain, (3) severe shock, (4) "significant" cardiac enlargement, [illegible] phlebitis, or lower extremity varicosities.

Our diabetic patients are usually in the "poor risk" group. Frequently ketosis is present As a group they are rather infrequently the subject of

[289] Lemly-Stone, Merrill, and Meneely Amer Jour Physiol, *184*, 555, 1955
[290] Wright Proc Am Fed Clin Res, *2*, 101, 1945
[291] Russek *et al* Jour Am Med Assn, *145*, 390, 1951

by thyroid ablation with radioactive iodine has been reported, but as yet no patients of the New England Deaconess Hospital have been so treated

Surgery in Coronary Artery Disease—Diabetic experience to date is such as to warrant an extremely careful appraisal of any surgical procedure for benefit of this condition Few diabetics have intractable angina over pro-

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tions in mind 4 diabetic patients have undergone the procedure Three of them had experienced at least one myocardial infarction associated with congestive heart failure. One of these, Case 19887, has been cited. Another Case 30063, was relieved of angina for one month, but then had acute coronary insufficiency, and now has the same degree of angina as before operation.

Experience with long-term use of dicoumarin derivatives in diabetics is too scanty for comment at this time

Hypoglycemia may produce various symptoms and signs indicating cardiac difficulty, such as changes in heart rate, blood pressure and rhythm. The production of angina pectoris and myocardial infarction must be extremely rare, and few cases of actual infarction are well documented [214-216] Low blood sugar levels may correlate with ECG findings but are usually reversed by glucose administration. Transitory changes noticed in schizophrenics are treated with large doses of insulin. No permanent changes in the ECG were found in cases of severe hypoglycemia at the Deaconess Hospital, particularly in a series of 25 young diabetics studied by Root.[218] Such observations apply in patients with healthy hearts and are not applicable to diabetics with proven coronary heart disease.

Insulin-induced hypoglycemia in 11 subjects with known angina has failed to reproduce angina despite electrocardiographic changes, which were

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Clearly, any adverse effect of hypoglycemia is not related to myocardial deprivation of glucose as a metabolite The capacity of this muscle to satisfy its needs for O_2 consumption by metabolizing lactate and fatty acid readily takes over when blood glucose levels are extremely low

Proven hypoglycemia as a cause of myocardial infarction has occurred at least once in our experience A 70 year old woman (Case 1520) was given insulin repeatedly elsewhere and entered the New England Deaconess

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1948 1953, none was found, but one woman (Case 7358) had a questionable episode of hypoglycemia at home as infarction was occurring She took

[214] Blotner New England Jour Med, 203, 709, 1930
[215] Gilbert and Goldzieher Ann Int Med, 25, 928, 1946
[216] Gandevia Med Jour Australia, 1, 33, 1954
[217] Root Ann Int Med, 11, 1340 1938
[218] Judson and Hollander Proc New England Cardiovasc Soc, 1953–54, p 21

Uncontrolled diabetes with ketotic or non-ketotic acidosis *after* myocardial infarction is an *absolute* indication for the use of insulin. In fact, insulin may be required in large amounts due to rapid development of moderate insulin resistance in the sense that 2 to 10 times the usual insulin dose may be required in a 24 hour period to bring blood sugars down to levels of 1.5 to 2 times normal. Such insulin needs are unrelated to food intake, and the diabetes may need the intensive treatment prescribed for typical diabetic coma.

When diabetes is uncontrolled in the sense that hyperglycemia without acidosis or ketosis occurs, experience in the "feel" of regulating the diabetes is extremely helpful. Lacking this, the most useful guide is a knowledge of previous behavior [illegible]
or the labile (usually [illegible]
sensitive to insulin [illegible]
stable diabetes will [illegible]
hypoglycemia. The latter type will make up the bulk of diabetic patients with coronary heart disease and myocardial infarction. To strive for blood sugars 1.5 times normal is a safe goal [illegible]

Prevention and Tre[illegible]
myocardial infarctio[illegible]
to restore disturbed [illegible]

(1) *Continuous Diabetic Control.*—In terms of its atherogenic potential, diabetes is *never* mild. The value of the blood sugar determination as a guide to intracellular metabolism has been reaffirmed by demonstrations indicating that its level often parallels that of lipid and protein fractions [illegible]

diabetic patients, and gradually rather than intensively. Although care is necessary to prevent frequent or severe hypoglycemia, elderly patients often have an elevated "renal threshold" so that continuous glycosuria, though slight, may indicate uncontrolled diabetes and should be avoided. Orinase may be useful in the patients responsive to this drug. Hypoglycemia may occur in the initial days of its use, but thereafter blood sugar levels should be maintained at normal levels with little if any risk of hypoglycemia.

(2) *Weight Reduction.*—The body weight of a diabetic should be below the average weight for his age after 35 years. Reduction in weight will improve the control of diabetes and reduce cardiac strain.

(3) *Reduction of Hypertension.*—Reversible hypertension should be sought and corrected. Whenever the diastolic hypertension is elevated or related to renal arteriolosclerosis special attempts should be made at its control.

(4) *Reduction in dietary fat* is clearly indicated, and measures previously mentioned should be undertaken to control hypercholesteremia.

(5) *Moderate exercise* and above all the *omission of smoking* must be prescribed. One may consider estrogen replacement in women at and following the menopause. The reduction of myocardial metabolic demands

by thyroid ablation with radioactive iodine has been reported, but as yet no patients of the New England Deaconess Hospital have been so treated.

Surgery in Coronary Artery Disease.—Diabetic experience to date is such

congestive heart failure. One of these, Case 19887, has been cited Another Case 30063, was relieved of angina for one month, but then had acute coronary insufficiency, and now has the same degree of angina as before operation.

Experience with long-term use of dicoumarin derivatives in diabetics is too scanty for comment at this time

Hypoglycemia may produce various symptoms and signs indicating cardiac difficulty, such as changes in heart rate, blood pressure and rhythm The production of angina pectoris and myocardial infarction must be extremely rare, and few cases of actual infarction are well documented [213–215]

consistent with hypokalemia [217]

Patients with uncontrolled diabetes may note distinct improvement in their angina when control is restored with insulin

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readily takes over when blood glucose levels are extremely low

Proven hypoglycemia as a ca...

at least once in our experience

insulin repeatedly elsewhere a

episode of hypoglycemia at home as infarction was occurring She took

Soc., 1953–54, p. 21

Uncontrolled diabetes with ketotic or non-ketotic acidosis after myocardial infarction is an *absolute* indication for the use of insulin. In fact, insulin may be required in large amounts due to rapid development of moderate insulin resistance in the sense that 2 to 10 times the usual insulin dose may be required in a 24 hour period to bring blood sugars down to levels of 1.5 to 2 times normal. Such insulin needs are unrelated to food intake, and the diabetes may need the intensive treatment prescribed for typical diabetic coma.

When diabetes is uncontrolled in the sense that hyperglycemia without acidosis or ketosis occurs, experience in the "feel" of regulating the diabetes is extremely helpful. Lacking this, the most useful guide is a knowledge [illegible]

hypoglycemia. The latter type will make up the bulk of diabetic patients with coronary heart disease and myocardial infarction To strive for blood sugars 1.5 times normal is a safe goal

Prevention and Treatment of Coronary Heart Disease.—The prevention of myocardial infarction is the goal to be attained. The objective should be to restore disturbed physiologic processes to as nearly normal as possible

(1) *Continuous Diabetic Control.*—In terms of its atherogenic potential, diabetes is *never* mild. The value of the blood sugar determination as a guide to intracellular metabolism has been reaffirmed by demonstrations indicating that its level often parallels that of lipid and protein fractions associated with all types of vascular disease in the diabetic. The control of hyperglycemia and glycosuria should be brought about by adjustments of diet and insulin which should be made with greater care than in ordinary diabetic patients, and gradually rather than intensively Although care is necessary to prevent frequent or severe hypoglycemia, elderly patients often have an elevated "renal threshold" so that continuous glycosuria, though slight, may indicate uncontrolled diabetes and should be avoided Orinase may be useful in the patients responsive to this drug Hypoglycemia may occur in the initial days of its use, but thereafter blood sugar levels should be maintained at normal levels with little if any risk of hypoglycemia

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(4) *Reduction in dietary fat* is clearly indicated, and measures previously mentioned should be undertaken to control hypercholesteremia

(5) *Moderate exercise* and above all the *omission of smoking* must be prescribed One may consider estrogen replacement in women at and following the menopause The reduction of myocardial metabolic demands

myocardial failure dominates the clinical picture. The true incidence of iron deposition in the myocardium is not known Unquestionably, many hemochromatotics exist without clinical evidence of heart disease

Among the 345 collected cases of hemochromatosis summarized by Sheldon,[220] myocardial failure was uncommon

At least 16 cases with autopsy proof of typical iron-containing myocardial lesions have been reported Fourteen of these were summarized by Swan and Dewar,[221] who added one proven at autopsy and another with the typical clinical picture A 34-year-old white woman with hemochromatosis of the heart proven at autopsy was discussed in a clinico-pathologic conference at Baylor University College of Medicine April 17, 1957 The development of auricular fibrillation with rapid downward course to death characterized the picture. Two such patients seen at the New England Deaconesss Hospital were a 30-year-old fisherman and a 36-year-old businessman. Each had rapidly progressive heart failure ending in death in one case with a typical distribution of the lesions of hemochromatosis in the heart, liver, pancreas, adrenals, skin, kidneys, spleen, lymph nodes, pituitary, thyroid, stomach, trachea and endothelial lining of many blood vessels The other recovered from heart failure and was last seen January 11, 1958.

Clinically, the development of rapidly progressive heart failure with a large, dilated heart simulating pericarditis with effusion and not responding to digitalization augurs a rapid demise Absence of valvular disease or evidence of coronary involvement, recent development of diabetes, and the finding of a dirty brown or gray skin should lead to diagnosis The liver may be enlarged and anasarca may be marked or absent. Chest pain, like that of angina, occurs with time but is of little diagnostic help

Rheumatic Heart Disease.—Rheumatic heart disease probably occurs with about the frequency which might be expected from the association of two relatively uncommon diseases At autopsy only 13 cases of rheu-

11,772)

later of undetermined cause

Miscellaneous.—Pericarditis in most instances has been part of a severe infection in the era before antibiotics, often with distant abscess formation or diabetic coma Chronic adhesive pericarditis has been proven at autopsy in one instance, Case 7763 Experience with bacterial endocarditis, erythema nodosum and disseminated lupus has been uncommon

[220] Sheldon Hemochromatosis, London, Oxford Univ Press, 1935
[221] Swan and Dewar Brit Ht Jour, *14*, 117, 1952
[222] Warren and LeCompte Loc cit, p 170

carbohydrate without relief, however, and on admission blood sugar was not low. Recovery occurred.

Myocardial Injury.—Hyperglycemia and glycosuria appearing with acute myocardial infarction have been reported frequently ever since the introduction of insulin. Short periods of hyperglycemia during acute episodes are frequent. However, studies by various authors have interpreted the hyperglycemia as an evidence of shock in the majority of patients. In patients followed up over a period of years, however, this apparent temporary hyperglycemia proved to be the introduction to permanent diabetes in one series.[39]

After experimental coronary occlusion, glycogen is lost from the infarcted muscle and lactic acid pours into the blood stream. These changes seem to have no measurable effect on blood levels of glucose.

Diabetics who develop congestive heart failure are often observed to have blood sugar elevations and to require more insulin. Whether this is related to glycogenolysis is uncertain as yet. Possibly it is due to vascular hepatic congestion with diminished capacity to store glucose, as in decompensated portal cirrhosis.

Severe shock due to various causes has been associated with elevation of blood levels

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Meissner. He found no central liver cell necrosis in 7, and only a "moderate degree" of it in 1. For comparison livers from 20 other autopsied diabetics in the series were studied, and showed no changes histologically that would distinguish them from the preceding group. The patient with the *highest* blood sugar had *no* significant clinical shock and *no* necrosis in the liver at autopsy. These results did not consider the 24 hour minimum interval during which Ellenberg and Osserman have said shock must be present to produce necros

had occurred

occurs rapidly

tected, or (2)

Results in our own patients have thus far made us favor the latter concept.

Although acute myocardial infarction appears to produce hyperglycemia and glycosuria in some individuals not subsequently showing any abnormality of carbohydrate metabolism, latent or borderline diabetes may readily be brought to light by such a severe test of insulin reserve. Persisting hyperglycemia and glycosuria (after two weeks) should be interpreted as diabetes. When these last only a few days, the individual should be observed regularly with blood sugar determinations.

Hemochromatosis and the Heart.—Hemochromatosis of the heart has been known for over 20 years, but proven cases of myocardial damage due to iron deposition are few. However, when damage occurs, the resulting

[39] Goldberger, Alesio and Wall. New York State Jour. Med., 45, 391, 1945.
[40] Bradley and Bryfogle. Loc. cit. p. 442.

Chapter 16

INFECTIONS IN DIABETES

ALEXANDER MARBLE, M.D.

A. INCIDENCE

AMONG the 818 diabetic patients studied by Warren and LeCompte[1] at post-mortem examination, infection, not including tuberculosis and syphilis, was the cause of death in 213. Further analysis of their data brings out the encouraging fact that whereas up to 1938, 38 per cent of deaths were attributable to infection, since then only 6 per cent have been due to this. Improvement may be ascribed to better control of diabetes and to the introduction of the sulfonamides and antibiotics. In the series of Warren and LeCompte, pneumonia was responsible for more deaths than any other localized condition, with 38 deaths from bronchial, and 10 deaths from lobar pneumonia.

The inter-relationship of diabetes and infections has always been involved and puzzling. All students of the disease agree that diabetes is made temporarily more severe by an infection, that the patient with uncontrolled diabetes has less than normal resistance and that an infection has often been the cause of death in a diabetic, particularly prior to the introduction of the chemotherapeutic agents and antibiotics. It is doubtful, however, that diabetes can be *caused* by an infection or made permanently more severe by one, except by certain rare infections of the pancreas itself or except in those individuals in which latent or unrecognized diabetes is activated by the stress of an infection. Moreover, the exact nature of the lowered resistance to infection which is common in uncontrolled diabetes, remains a problem about which little is known.

The diabetic is particularly susceptible to pulmonary tuberculosis and to infections of the urinary tract and skin. Among the 818 cases in the series of Warren and LeCompte referred to above, there were 18 deaths due to tuberculosis and 13 to infections of the urinary tract. The decreased resistance to the tubercle bacillus is probably related to the bodily insult of acidosis. (See pages 376 and 568.) This is a possible explanation, too, for the high incidence of urinary tract infections. The increased susceptibility of the skin to infection is probably not dependent upon its high sugar content, although conceivably may be related to a low glycogen content.[2]

Throughout the present discussion, comments regarding resistance to infection apply in general to uncontrolled diabetes since with proper treatment, the response of the diabetic to infection approaches the normal.

[1] Warren and LeCompte. P. 127, Loc. cit., p. 170.
[2] Bayne-Jones. Bull. New York Acad. Med., *12*, 278, 1936.

Polyarteritis nodosa has occurred in three cases. In one involvement of the heart was demonstrated at autopsy.

G. CEREBRAL ARTERIOSCLEROSIS

Unlike the striking incidence of and morbidity from arteriosclerosis obliterans in the peripheral vessels and from coronary atherosclerosis, cerebrovascular arteriosclerosis shows no increased prevalence in diabetic as compared to non-diabetic patients. Its frequency may be seen from Table 84, page 483

Treatment in the main continues to be supportive and does not differ from that used for non-diabetic patients. The cerebrum is far more dependent upon glucose for its normal metabolism than is the myocardium, and severe or prolonged hypoglycemia can produce serious injury. Special measures for the relief of so-called vasospastic attacks or to protect the portion of the brain around the infarcted area from further ischemia and destruction have been attempted with the usual agents, such as nicotinic acid, papaverine, and histamine. No striking benefits have been noted, nor have carbon dioxide or stellate ganglion blocks been sufficiently beneficial to warrent their continued use in diabetics. Anticoagulants have been used in a few cases with benefit.

(1) lessened production of endogenous insulin· (2) increased production of hormonal antagonists, (3) destruction of insulin; (4) interference with the storage and utilization of glycogen

Lessened Production of Insulin.—Williams and Dick[13] found that glycosuria occurred in 41 per cent of patients with acute infectious diseases The largest average amount occurred with influenza Temporarily diminished tolerance for carbohydrate is shown by sugar tolerance curves in acute infectious diseases and in experimental inoculation in animals. (See page 165) Labbé[14] demonstrated a lowered carbohydrate tolerance in pneumonia, and MacLean and Sullivan[15] in encephalitis, tuberculosis, meningitis and measles

disturbance seen might well be due to effect on the liver It is true that

non-diabetic patient who died from lobar pneumonia In this patient most of the islet cells were necrotic or showed some evidence of injury.

Increased Production of Hormonal Antagonists.—Although increased production of insulin antagonists as from the pituitary, adrenal and thyroid glands would theoretically explain the temporary worsening of diabetes during infections, no definite evidence along this line has been brought forth. Indeed, it would seem likely that although during the early stages of an acute infection stimulation of the adrenal cortex might occur in response to stress, one would anticipate that as the infection proceeded, hypersecretion of adrenal cortical hormones would subside and if the infection were severe and long-cont

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Destruction of Insulin —The actual destruction or chemical inactivation of insulin in circulation is believed by some to be possible Trypsin or toxins produced by leukocytes, pus and bacteria may destroy it *In vitro* pus cells destroy insulin but this has not been proved *in vivo*

Rabinowitch[18] suggested that an insulin destroying enzyme is produced during infections On the basis of studies of sugar tolerance tests of diabetic patients during infection with and without fever and with varying degrees of fever, he concluded that it is the infection, not the fever, that causes the impaired tolerance

[13] Williams and Dick Loc cit , p. 165
[14] Labbé Bull et mem Soc méd d hôp de Paris, 49, 1358, 1925
[15] MacLean and Sullivan Am Jour Dis Child , 37, 1146, 1929
[16] Warren and LeCompte Page 122, loc cit , p 170
[17] Lawrence and McCance Brit Med Jour , 1, 749, 1931 See also Lawrence and Buckley Brit Jour Exp Path , 8, 58, 1927, and Evans and Zeckwer Ibid , 8, 280, 1927
[18] Rabinowitch Canad Med Assn Jour , 26, 551, 1932

Williams,[3] in an analysis of experience in doctors' offices and in general hospitals, concluded that "it is extremely doubtful that diabetes increases

[illegible]

may appear to be a gain rather than a loss in carbohydrate tolerance, just as in diabetes complicated by tuberculosis. Examples were cited by Root.[4]

Pulmonary tuberculosis, infections of the urinary tract and infections of the skin in diabetes are discussed in detail on pages 507, 522, and 563, respectively.

B INFECTION AS AN ETIOLOGICAL FACTOR

Published reports vary considerably as to the relative frequency of acute infections prior to the onset of diabetes. In our juvenile cases, in whom one would expect the highest correlation, 90 of 100 children in one series studied had no significant infection within a year of onset. Severe and prolonged infections under close observation in general hospitals, especially in surgical wards, are common and yet the development of diabetes in such cases is so rare as to be an occasion for great surprise. These are practical reasons why we do not consider infections of great etiological importance (See page 75.) Lande,[5] recorded the same belief. In contrast to this view John[6] found that 20 per cent of his juvenile cases had an infection within two months of onset. Barach,[7] too, found a high incidence of infection. An increasing incidence of diabetes after epidemics of influenza was reported by Jones.[8] Lierle and Potter[9] found that low-grade tonsillitis and colds occurred frequently prior to onset. Bertram[10] stated that in a large percentage of his cases diabetes became manifest during an infection. How-

[illegible]

One would admit that the development of diabetes following acute pancreatitis or during a chronic pancreatitis[11,12] would not be surprising. However, even this is rare. Among our patients are two cases (37181 and 38142) in whom the onset of diabetes appeared to be associated with acute pancreatitis. For further discussion see page 170.

C CAUSE OF LOWERED TOLERANCE FOR CARBOHYDRATE DURING AN INFECTION

A lowered tolerance for carbohydrate during infections either in the diabetic or non-diabetic theoretically might be due to one of four causes:

[3] Williams Jour Am Med Assn, *118*, 1357, 1942
[4] Root New England Jour Med, *210*, 127, 1934
[5] Lande Klin Wchnschr, *10*, 359, 1931
[6] John Ann Int Med, *8*, 198, 1934
[7] Barach Arch Int Med, *39*, 636, 1927
[8] Jones, quoted by von Noorden Die Zuckerkrankheit und ihre Behandlung 8th ed, *Berlin, Julius Springer, 1927*
[9] Lierle and Potter Arch Otolaryngol, *14*, 432, 1931
[10] Bertram Med Welt, Nos 30, 32, 1936
[11] King Med Clin North Amer, May, p 883, 1919
[12] Aarseth Nord med, *44*, 1567, 1950 Abstracted in Diabetes Abstracts, *10*, 7, 1951

decrease the bacterial power of the blood or affect its opsonic index. Hirsch-Kauffmann and Heimann-Trosien[24] observed that streptococci, pneumococci and influenza bacilli grew better on blood agar plates made with blood from a patient in diabetic coma than on ordinary blood agar, but there was no effect from hyperglycemic blood from non-coma cases, from the addition of dextrose and acetone *in vitro*, or from cases of experimental hyperglycemia, lipemia and acidosis. Moen and Reimann[25] consider the liability to infections of patients with poorly controlled diabetes to be due

[illegible]

Mosenthal[27] regards polyuria and dehydration accompanying prolonged and marked glycosuria as responsible for the diminished resistance to

[illegible]

tients, and Horster,[30] depancreatized dogs, found that the amount and activity of the complement of the blood serum did not differ from that of normal blood. However, Bayer and Form[31] stated that following removal of the pancreas there occurred a decrease in hemolytic complement which could be temporarily restored to normal by the injection of insulin and glucose.

Moen and Reimann,[32] in the study previously referred to, found that the production of typhoid agglutinins was lower in patients with diabetes than in normal individuals. In proportion to the severity of the disease, similar results were reported by Richardson.[29] On the other hand, Wale and Madders[33] found that blood from diabetic patients had essentially the same amount of natural staphylococcal antitoxin and that following toxoid treatment antitoxin increased to practically the same degree as in

[illegible]

the nutritional state and the blood-sugar level in influencing the development of agglutinins after typhoid vaccine. He produced hyperglycemia in rabbits by injecting adrenalin and lowered the nutritional state by starvation. He concluded that the state of cellular nutrition was more impor-

[24] Hirsch-Kauffmann and Heimann-Trosien. Klin. Wchnschr., *5*, 1655, 1926.
[25] Moen and Reimann. Arch. Int. Med., *51*, 789, 1933.
[26] Pillsbury and Kulchar. Am. Jour. Med. Sci., *190*, 169, 1935.
[27] Mosenthal. Jour. Am. Med. Assn., *105*, 484, 1935.
[28] Bayne-Jones. Loc. cit., p. 451.
[29] Richardson. Jour. Clin. Invest., *12*, 1143, 1933.
[30] Horster. Deutsch. Arch. f. klin. Med., *176*, 502, 1934.
[31] [illegible] *52*, 1338, 1926.

[illegible] *17*, 279, 1933.

Interference With the Storage of Glycogen.—The work of Fetzer[19] regarding the relation between carbohydrate metabolism and experimental staphylococcus infection in rabbits suggested that the toxins of the staphylococci reduced the glycogen content of the liver. The effect was diminished by treating animals with dextrose. Fetzer concluded that the increased resistance of the dextrose animals against staphylococcus toxin may be related to their greater glycogen reserves.

In a discussion of insulin resistance due to infection, Greene and Keohen[20] mention various theories which have been advanced to explain such resistance. Studies were carried out with diabetic patients in an attempt to ascertain the effect on the insulin requirement of infections, idiopathic fever, administration of foreign proteins, hyperthermia produced in a fever cabinet and the administration of histamine and epinephrine. The results were inconclusive in that an increase in insulin requirement did not develop in all cases of infection or fevers or in response to histamine or epinephrine. [illegible] an increase in insulin requirement may be anticipated.

D DECREASED RESISTANCE TO INFECTION IN DIABETES

Since the introduction of insulin, and particularly the long-lasting depot insulins, treatment has been so improved that excellent control of diabetes is possible with almost all patients. In those with whom this is obtained and to whom an adequate diet is supplied, clinical resistance to infection appears to approach the normal.[21] However, even today in those patients whose diabetes is poorly controlled, the decreased ability to overcome infections cannot be denied. In their article on this subject, Marble, White and Fernald[22] discussed certain factors as *possible* causes of the lowered resistance to infection in diabetes, these are as follows:

(1) Increased sugar content of blood and tissues. (2) Decreased activity of blood elements associated with resistance to infection; (a) subnormal activity of complement, (b) subnormal phagocytizing capacity of leukocytes, (c) subnormal bacteriostatic and bactericidal action of whole blood. (3) Inadequate functioning of fixed tissue cells. (4) Lowered capacity of tissues to react to antigenic stimuli. (5) Lowered state of general cellular nutrition.

Formerly it was thought that the increased sugar content of the blood and tissues seen in diabetic patients favored the growth of bacteria, particularly staphylococci. Present-day opinion does not favor this explanation. Handmann[23] found that *in vitro* staphylococci grew no better on blood containing 0.5 to 1 per cent sugar than on normal blood, furthermore, the addition of glucose to blood within the limits found in diabetes did not

[19] Fetzer. Arch. f. Hyg., *107*, 255, 1932.
[20] Greene and Keohen. Jour. Amer. Med. Assn., *121*, 173, 1943.
[21] Wohlenberg. München. med. Wchnschr., *88*, 883, 1941.
[22] Marble, White and Fernald. Jour. Clin. Invest., *17*, 423, 1938.
[23] Handmann. Deutsch. Arch. f. klin. Med., *102*, 1, 1911.

Ingraham,[40] in their standard text on syphilis, state the opinion that diabetes due to syphilis, if it exists at all, must be rare Clinicians of such experience as Labbé and Touflet[41] reported no definite cure of diabetes by anti-syphilitic therapy

Among the 818 diabetic patients studied by Warren and LeCompte[42] at post-mortem examination, there were
hemorrhage from a syphilitic ulcer of
rupture of an abdominal aneurysm
no pancreas in the series did it seem likely that syphilis could be responsible for the change present Williams[43] stated that, excluding congenital syphilis, syphilitic pancreatitis was not found a single time among 4800 routine autopsies

The study by McDaniel, Marks and Joslin[44] was concerned with 17,500 glycosuric patients seen between 1897 and 1939, among whom 15,095 fulfilled the criteria of true diabetes mellitus. Of this number, 258 cases had proven syphilis. Therefore, the incidence of syphilis in the diabetic group was lower than that reported for diabetes in the world literature, which varied from 0 16 per cent to 11 5 per cent. It is significant to note that at the time of the study the incidence of 1 7 per cent of syphilis in diabetics

[illegible] per cent were identified by serology alone.

In 1931 Root and Stuart[47] reported the results of a study of the specificity of blood tests for syphilis among diabetic patients in our clinic Among 1078 Wasserman, Hinton and Kahn tests they found no falsely positive reactions which could be ascribed to variations in the blood sugar or blood cholesterol or to acidosis Our clinical experience in the twenty-seven years since then bears out that finding

Of the 258 cases reported by McDaniel *et al*, 188 were males and 70 females In most instances there were no physical signs or symptoms of syphilis, 86 8 per cent had reached the latent stage at the time of examination No difference in diabetic heredity was apparent, since 20 7 per cent of the diabetics with syphilis had a positive family history of diabetes as compared with 24 5 per cent in a control group of 6357 diabetics Among the entire series, 60 per cent had received some anti-luetic treatment but

[40] Stokes Beerman and Ingraham Modern Clinical Syphilology, 3rd ed, Philadelphia W B Saunders Co, 1944

[41] Labbe and Touflet Ann de méd, *14*, 367, 1923

[42] Warren and LeCompte Loc cit, p 107

[43] Williams New York State Jour Med, *41*, 232, 1941

[44] McDaniel, Marks and Joslin Loc cit, p 456

[45] Merritt and Moore New England Jour Med, *219*, 874, 1938.

[46] Hinton and Davies Suppl No 9 to Venereal Disease Information, Washington, Government Printing Office, p 172, 1939

[47] Root and Stuart New England Jour Med, *204*, 1179, 1931

tant than the level of blood sugar in determining the antibody response. Richardson[15] observed in normal rabbits and depancreatized cats a significant correlation between the amount of glycogen in the liver and the survival time of the animals after intravenous inoculations with bacteria, including especially the staphylococcus aureus. In poorly nourished, depancreatized cats with a decreased liver glycogen, a low agglutinative titer was found after injection of typhoid vaccine. Alterations in the sugar, cholesterol, protein, and albumin content of the blood did not influence the dissemination of bacteria. Acidosis appeared to increase the frequency of this dissemination. Flick *et al.*,[16] testing the antibody response of diabetic patients to typhoid immunization, found a positive correlation between the antibody response and the serum albumin concentration.

Marble, White and Fernald[17] found that fresh defibrinated blood and heparinized whole blood of diabetic patients possessed essentially the same phagocytic, bacteriostatic and bactericidal power against selected strains of streptococci as blood from normal controls. The results in individual patients could not be correlated with the duration, severity or state of control of the diabetes. Their findings suggested that diabetic patients who successfully overcome infections thereby develop specific immunity to approximately the same extent as individuals without diabetes. Cruickshank and Payne[18] found that a Type II pneumococcus, inoculated into whole blood of rabbits with alloxan diabetes and incubated *in vitro*, grew much more rapidly than in normal blood. However, when plasma alone was inoculated, growth tended to be heavier in the normal plasma. They therefore suggested that there may be a defect in the leukocytic defense of animals with alloxan diabetes.

In summary, it must be conceded that the causes for lowered resistance to infection in uncontrolled diabetes are still not apparent. It is certainly related to the malnutrition, lowered glycogen content of the liver, dehydration and acidosis which characterize the patient with poorly controlled diabetes. As to the exact mode and site of operation of these factors little information is available.

E. SYPHILIS AND DIABETES

[illegible]

bined syphilis and diabe [illegible] in 1940 failed to show any [illegible] betes. *The history and* [illegible] the diabetes in patients with syphilis were just the same as for any patient with diabetes. It was impossible to recognize any characteristics of a clinical condition termed "syphilitic diabetes." Stokes, Beerman and

[15] Richardson. Ibid., *19*, 239, 1940.
[16] Flick, Ketterer, Wohl and Waife. Am. Jour. Med. Sci., *221*, 71, 1951.
[17] Marble, White and Fernald. Loc. cit., p. 451.
[18] Cruickshank and Payne. Bull. Johns Hopkins Hosp., *84*, 334, 1949.
[19] McDaniel, Marks and Joslin. Arch. Int. Med., *66*, 1011, 1940.

and the need for extra insulin quickly abate If the patient has not been

If Benedict test of urine is	Red or Orange	Yellow	Yellow-green	Green or Blue
Give units	8	6	4	0

The size of the doses used in the above formula may need to be varied considerably, depending upon the severity of the diabetes, its present degree of control, the character of the infection, and the age of the patient If it is found that appreciable amounts of supplementary insulin are needed before meals, the basic dose of both rapidly and slowly-acting insulins given before breakfast should be gradually increased a few units at a time

In certain patients not previously receiving insulin, rapidly-acting insulin may be administered at frequent intervals according to urine tests throughout the day, giving it every *three or four hours* by a schedule such as the following

If Benedict test is	Red	Orange	Yellow	Yellow-green
Give units	20	16	12	8

However, very early in treatment a depot insulin such as the NPH or lente type may be started in a single dose daily before breakfast and the amount gradually adjusted It should be possible within twenty-four to forty-eight hours to have the patient on a schedule in which NPH or lente insulin with or without an accompanying dose of regular or crystalline insulin before breakfast with supplementary doses only before the noon and evening meal

Sulfonamide and Antibiotic Therapy.—Diabetic patients with infections have shared with other sick persons in the better treatment and lower mortality rate made possible by the introduction of the sulfonamides and

to recount our experience with these drugs, because it parallels that of

have diminished in incidence, because the use of antibiotics in early stages may abort these dreaded infections Even if there is early neglect by the patient, intensive antibiotic treatment often obviates the necessity for

with no consistent influence on the diabetic condition. Causes of death in 130 diabetics with syphilis as compared with that in 4474 diabetics showed no significant difference. Only 3 cases of congenital syphilis occurred among the 258 patients.

F. THE MANAGEMENT OF INFECTIONS IN DIABETES

An infection makes a diabetic worse. This rule is so exact that one can often make a safe prediction upon the condition of the infection by the course of the diabetes and, conversely, whenever a diabetic does badly, one must search for an infection (or other complications such as hyperpituitarism, hyperthyroidism, hemochromatosis or cancer of the pancreas). The effect of a carbuncle upon the diabetic process is an excellent example. With its advent a diabetes almost quiescent for years may become intensely severe, but with its subsidence resume its mild character.

Diet and Insulin.—Unless promptly and adequately treated, an infection may lead to acidosis, due largely to the fever and resulting increase of metabolism. The insulin requirement will almost invariably increase. Sufficient insulin should be given to secure satisfactory control of the diabetic condition. The diet should be simple and must often be more concentrated than usual because of the patient's illness. From 100 to 200 grams of carbohydrate should be taken daily.

Carbohydrate in the form of oatmeal or other cereals, fruit juices, well-cooked or pureed vegetables, protein as eggs, fish and chicken, and fat in the form of cream will tide over many emergencies. A simple diet is given in Table 81.

TABLE 81.—A TEMPORARY SUBSTITUTE FOR STANDARD DIET

(C 155, P 75, F 80, 1640 cal.)

Useful in the Treatment of Patients with Infections or Digestive Disturbances

*Food**	*Carbohydrate, gm*	*Protein, gm*	*Fat, gm*
Milk, 960 cc. (1 quart)	48	32	32
20 per cent cream, 60 cc. (2 ounces)	2	2	12
Bread, 90 grams (3 slices)	45	8	0
Oatmeal, 30 grams (1 large saucerful)	20	5	2
Egg, 2	0	12	12
Meat, lean 60 grams (2 ounces)	0	16	10
Butter, 15 grams	0	0	12
Orange juice, 400 grams	40	0	0
	155	75	80

* For a child cream could be omitted and butter reduced.

During active infections insulin should be given in doses large enough to keep the diabetic condition under good control although during the short period of acute infections, absolute sugar-freedom is not necessary or indeed, wholly desirable, since at any time during an infection, recovery may begin

Chapter 17

THE DIGESTIVE SYSTEM IN DIABETES

ALEXANDER MARBLE, M D

A THE TEETH AND GUMS

Dental Caries and Periodontal Disease.—It is regrettable that the teeth of adult diabetic patients are often poor. This is important because poor teeth can complicate the treatment of diabetes and oral sepsis may make diabetes worse Taking diabetic patients as a whole, however, the frequency of caries probably is no greater than in non-diabetic persons Surveys, made among large groups of individuals in the general population, have invariably shown an extraordinarily high incidence of dental abnormalities

(1) Dunning and Hinson[1] of the Harvard School of Dental Medicine found that although 234, or 84 8 per cent, of 276 diabetic children (aged six to seventeen years) were in need of some type of dental care, the incidence of missing, filled or carious teeth and of periodontal disease was no greater than that of a control group of non-diabetic children of comparable ages It was noted that in general those children needing no dental atten- [illegible]

[illegible]

diabetes on the average for 19 5 years. Because of lack of a control group, no valid correlation of the findings with diabetes could be made except that [illegible]

[illegible]

Knishkowy, Person and Pollack[5] in a study of the oral cavity in 149 treated diabetics, found that the incidence of acute inflammation and infection was low, and that in general the type and degree of abnormalities noted in the diabetic group were about the same as in non-diabetics

[1] Dunning and Hinson Personal communication
[2] Robison Harvard Dent Alumni Bull, *14*, 17, 1954
[3] Dunning and Klein Jour Amer Dental Assn, *31*, 1632, 1944
[4] Robison Loc cit p 461
[5] Knishkowy, Person and Pollack Jour Mt Sinai Hosp, *17*, 192, 1950

radical surgery even if the carbuncle has reached a well-marked stage. Under the protection of antimicrobial agents it is now possible to carry out more conservative types of surgery in the diabetic, thus, in many patients with relatively poor circulation a transmetatarsal amputation is possible, giving the patient a useful foot and lower leg. With the use of organism-specific antibiotics in liberal dosage, amazing benefit is secured in acute infections of various types just as in the non-diabetic. Some years prior to the advent of these newer drugs when the mortality among diabetic patients was 12 to 15 per cent, McKittrick[19] made the prediction that if it were possible to avoid that share of mortality due to infections, the rate should fall to the neighborhood of 5 per cent. Our experience during the era of the antibiotics has proven this prediction to be entirely correct.

[19] McKittrick: New England Jour. Med., *235*, 929, 1946.

dental caries [10]

Using insulin if necessary, it is possible to allow diets which from a nutritional standpoint are the equal or the superior of average, unselected diets It is desirable, and indeed necessary, to include milk and other dairy products in the dietary of every diabetic, young and old. To insure an adequate calcium intake the diet of every adult diabetic should contain at

There is another reason why good treatment of diabetes should automatically include proper care of the teeth Perhaps more than any other large group of individuals in the country, diabetics visit their doctors often and have frequent physical examinations If both physician and patient are alive to their responsibilities, early defects are noted and treatment

must be kept under control Second, patients must be drilled in the proper local care of their teeth and gums They must be taught to brush their teeth properly twice daily and see their dentist every three to six months The rules listed below have been found useful

1 Use a small toothbrush with tufts well separated Have two brushes, and alternate each time you brush your teeth Replace brush when bristles become too soft

5 Have your teeth cleaned and examined by a dentist or dental hygienist every three to six months. Keep all cavities filled

Suggestions Regarding Dental Extractions.—Dr E J. Durling has outlined the rules followed at the dental clinic at the New England Deaconess Hospital regarding extractions

[10] Drain and Boyd Jour Amer Dental Assoc, 17, 738, 1930

Rudy and Cohen[6] reported upon a two-year experience in the diabetic clinic of the Beth Israel Hospital in Boston. Of 403 patients, 138 were [illegible] dren and 3 young [illegible] ad excellent teeth [illegible] In Mosenthal's[1] experience the incidence of caries and pyorrhea was related to the degree of control of diabetes

In a study of 43 patients from eleven to twenty-five years of age with diabetes of ten to twenty years' duration, Kent[8] found 18 with no fillings [illegible] or fillings had had diabetes since the age of eight years or younger. This may be significant because the period of high caries susceptibility of most young adults lies between the ages of seven and twenty years of age It has been stated that if the onset of diabetes occurs during the middle or latter part of this high caries susceptibility period, many carious and infected teeth are found, but that this process is often arrested when the control of diabetes is satisfactorily maintained. A survey of another group of diabetic boys and girls between the ages of seven and sixteen years—the high susceptibility period just noted—showed that 26, or 20 per cent, had no fillings or cavities or had lost no teeth due to dental decay. In all patients in this group diabetes had been discovered between the ages of one and nine years, before many of the permanent teeth had erupted Among another group of 30 diabetic patients between the ages of two and seven years 80 per cent were free from dental caries This experience would appear to substantiate the statement that if the onset of diabetes occurs before the age of nine there is a good chance that these patients can retain their teeth and have healthy mouths

Influence of Control of Diabetes.—The above comments should not be taken to imply that consistently poor control of diabetes presents no hazard to dental health Clinical experience indicates that this is certainly not so. Even though surveys suggest that in general dental caries is not more common in diabetics than non-diabetics, periodontal disease is, especially if the diabetes is poorly controlled During and immediately following diabetic coma—the most advanced stage of poor control—the teeth may become loose but tighten when the diabetic condition is brought back under control. Although tartar deposits, gingivitis and pyorrhea are commonly found in the mouths of adult patients whose diabetes is controlled, these changes are not so progressive as in those patients with poorly controlled diabetes [illegible] patient with uncontrolled diabetes of [illegible] to dental caries and pyorrhea[9] Ac[illegible]ydration and at times a negative nitrogen balance, there is the factor of lowered resistance to infection which occurs in uncontrolled diabetes With this, and with lowered vitality of

of advice by the physician is necessary. Patients unless continually encouraged are apt to drift back into slipshod habits of living, because for the moment such a course seems easier

In addition to diet, exercise and regular habits it is often helpful to have the patient take 1 or 2 glasses of warm or hot water in the morning before breakfast Often the stimulus from this, plus the gastro-colic reflex provided by the meal, will enable the patient to secure shortly after breakfast an evacuation if sufficient time is regularly left for this

When upon special indication a cathartic is desired, any of the standard laxatives may be used We ordinarily use the compound rhubarb pill Often ½ to 1 ounce of mineral oil at bedtime is helpful but should not be

certain rhubarb pills the presence of peppermint or salicylate may lead to the excretion in the urine of an acid which may be confused with diacetic acid and thus lead to unwarranted alarm Citrate of magnesia as sold in liquid form is contraindicated because of the sizable quantity of syrup which the U.S P preparation contains (60 cc of syrup in a total volume of 350 cc)

C DIARRHEA

Importance.

may lead to diabetic coma because with abstinence from food there is often neglect to take insulin, patients often erroneously reason that they should not take any insulin because they are not eating or retaining food On the other hand, diarrhea may provoke a severe insulin reaction because the effectiveness of insulin may be increased by the low metabolism and the non-absorption of carbohydrate Consequently, diarrhea in a diabetic should be regarded seriously. One benign cause is that of irritation by coarse, bulky vegetables in a patient who has lived on a concentrated diet before the institution of diabetic treatment With such patients the return to a concentrated diet for a few days usually clears up the difficulty One must not forget, however, that the diarrhea may have no such simple and easily remedied cause In diabetics as in non-diabetics diarrhea may be due to cancer of the lower bowel, ulcerative or mucous colitis, amebic dysentery, typhoid fever or other serious complicating diseases In any diarrhea which does not respond quickly to simple measures, one should try to ascertain the true cause

Anacidity. Absence of free hydrochloric acid from the gastric juice may in some individuals—diabetic and non-diabetic—be associated with diar-

incidence of anacidity If one combines the published data of Bowen and

1. The diabetic condition of the patient should be under good control. Close liaison should be maintained between the physician and the oral surgeon.[11]
2. Local anesthesia as with novocaine is preferable since this does not necessitate omission of food prior to its administration nor does it interfere [illegible]

3. The technique used should be as nearly aseptic as possible.
4. Care should be taken to cause as little trauma as possible and with this in mind only a few teeth should be extracted at a time.
5. To avoid postoperative bleeding, all sockets or wounds should be carefully sutured.
6. Consideration should be given to the use of penicillin or other antibiotic at a suitable interval prior to the extraction, especially in cases of infection.

Following the extraction of infected teeth the amount of sugar in the urine may increase temporarily and require additional insulin for a short time. Consequently, out-patients should be instructed to test the urine three or four times daily for two or three days following extractions and to adjust the insulin dosage accordingly.

B. CONSTIPATION

Although constipation is probably no more frequent among diabetic patients than among a similar group of non-diabetic individuals, it is a common complaint especially among older patients. The diabetic diet is not in itself constipating. The liberal amount of roughage afforded by vegetables along with the use of fruit at each meal stimulates intestinal peristalsis. The diabetic is encouraged to exercise, since physical activity not only tends to lower the blood sugar when there is an adequate insulin supply but also is beneficial in maintaining regular bowel habits.

It is unfortunately true, however, that among diabetics, as among non-diabetics, one sees too many people who are, or who fancy that they are, constipated. When for any reason a patient begins with purgatives, often such drugs are employed in increasing amounts with the eventual result that a cathartic habit is established. That patients who have been constipated and have taken laxatives regularly for years and years can be cured of their difficulties and their bowels returned to normal function has been amply shown by Jordan,[12] Brailey,[13] Bauer[14] and others.

In the treatment of constipation as in the management of most diabetic problems, regularity is the keynote. Regularity in eating, in the taking of fluids, in sleeping, in exercise, in the time of going to the toilet—this is the most helpful, single direction that one can give. Constant repetition

should be given intravenously. Unless insulin is already being given to the point of tolerance, it is well to give 8 to 12 units of crystalline insulin by separate injection at the time that the infusion of dextrose is given intravenously Diarrhea may cause either a decrease or an increase in insulin requirement If more insulin is needed, it is safer to give it in smaller doses more frequently.

As symptomatic, nonspecific treatment, one may use one teaspoonful of bismuth subcarbonate with or without one teaspoonful of paregoric after each loose movement up to three doses in twenty-four hours

Diabetic Diarrhea —Diabetic diarrhea as a manifestation of neuropathy affecting the autonomic nervous system is a distressing complication which is often difficult to treat For a full discussion, see page 500

D. ULCER: GASTRIC AND DUODENAL

Incidence.—The incide [illegible] considerable discussion [illegible] ess Hospital in the ten-y [illegible] approximately 135 separate cases of peptic ulcer, 14 gastric and 121 duodenal, among 20,094 total admissions, an incidence of 0 66 per cent In the seven years from 1951 through 1957, there were 270 admissions for peptic ulcer, 58 gastric and 212 duodenal, among 18,439 total admissions, an incidence of 1 46 per cent Among Lande's[29] 2,100 diabetic patients there were 22 with ulcers of the stomach or duodenum Falta[30] had not [illegible]

[illegible] sidered the adjusted incidence of peptic ulcer in diabetic patients is about the same as that in the general population

A study by Wood[34] of 94 patients with peptic ulcer observed on the Joslin Clinic service at the New England Deaconess Hospital from 1934 to 1944, showed that the disease occurred in 68 males and 26 females with ages ranging from twenty-three to seventy-four years at the beginning of ulcer symptoms However, ulcer symptoms began usually in the older age *groups and actually 73 patients were past the age of forty* when symptoms

[29] Lande Kln Wchnschr, *10*, 359, 1931
[30] Falta P 116, loc cit, p 79
[31] Wilder P 303, loc cit, p 71
[32] Rothenberg and Teicher Am Jour Digest Dis and Nutrition, 5, 359, 1931
[33] Spiegelman and Marks Amer Jour Pub Health, *36*, 26, 1946
[34] Wood Am Jour Digest Dis, *14*, 1, 1947

Aaron,[14] McPherson,[16] Wiechmann and Elzas,[17] Root,[18] Rabinowitch, Fowler and Watson,[19] Wohl,[20] Moore[21] and Klein,[22] one finds that among 399 diabetic patients there were 131, or 32.8 per cent, with complete anacidity. *These data are of interest but the anacidity alone may well bear no causal relation to diarrhea when it occurs.* Bloomfield and Pollard[23] after a careful and extensive study of gastric anacidity, concluded that this secretory defect probably does not cause diarrhea and that "in the occasional case associated with diarrhea, it is probable that coincident bowel lesions or disorders play an important part."

Insufficiency of External Secretion of Pancreas. [illegible]

[illegible] diabetes, one must agree with Falta[28] that in the great bulk of diabetic patients, even in those with the disease in severe form, the digestion and absorption of food seem to take place in a completely normal fashion. Falta pointed out that in the pre-insulin days patients were fed enormous amounts of fat and protein with astonishingly little difficulty therefrom. *This clinical experience is in keeping with the results* (as yet unpublished) of a recent study made on our patients with the cooperation of Dr. Harry Shwachman in whose laboratory the determinations of pancreatic enzyme activity were carried out. Of 35 patients aged 17 to 67 years with duration of diabetes of 6 to 34 years, no instance of significant reduction in duodenal ferments was noted except in 6 patients with pancreatic calculi. In this special small group greatly diminished or absent enzyme activity was found. All 6 patients gave a history at one time or another suggesting chronic pancreatitis, *i.e.*, recurring episodes of diarrhea, abdominal distress, etc.

[illegible] concentrated and consist of foods which are soft and easily tolerated. Leafy, green vegetables, raw fruit and cold and iced liquids should be avoided. If the diarrhea is simple in nature and of brief duration, no great problem is posed. Return to a normal diet may be made gradually as the tolerance of the patient dictates.

If the diarrhea is severe and particularly if food and fluids are not retained when given by mouth, 5 per cent dextrose in water or salt solution

[14] Bowen and Aaron. Arch. Int. Med., *37*, 674, 1926.
[16] McPherson. Glasgow Med. Jour., *107*, 340, 1927.
[17] Wiechmann and Elzas. Deutsch. Arch. f. klin. Med., *164*, 163, 1929.
[18] Root. Jour. Am. Med. Assn., *96*, 928, 1931.
[19] Rabinowitch, Fowler, and Watson. Arch. Int. Med., *47*, 384, 1931.
[20] Wohl. Jour. Lab. and Clin. Med., *17*, 22, 1931.
[21] Moore. Brit. Med. Jour., *1*, 363, 1932.
[22] Klein. Deutsch. Arch. f. klin. Med., *173*, 359, 1932.
[23] Bloomfield and Pollard. Gastric Anacidity, New York, The Macmillan Company, p. 86, 1933.
[24] Jones, Castle, Mulholland and Bailey. Arch. Int. Med., *35*, 315, 1925.
[25] Labbé and Rechard. Arch. d. mal. de l'app. digest., *16*, 865, 1926.
[26] Okada *et al.* Proc. Imperial Acad. (Japan), 4, 134, 1928.
[27] Walodin. Arch. f. Verdauungskrankh., *49*, 168, 1931.
[28] Falta. P. 119, loc. cit., p. 79.

or about diverticula such as these can, by extension, cause chronic p
creatitis and diabetes[36] was not demonstrable in these cases

F. GASTRO-INTESTINAL HEMORRHAGE IN THE DIABETIC

Hemorrhage into the gastro-intestinal tract of diabetic patients oc
very readily As mentioned above, gross hemorrhage from peptic ul
occurred in 26 6 per cent of our cases

G CANCER OF THE GASTRO-INTESTINAL TRACT

For a discussion of cancer of the gastro-intestinal tract and particul
cancer of the pancreas in association with diabetes, see Chapter 24, p

H SPECIFIC DISORDERS OF THE LIVER IN DIABETES

Hepatitis —Among 20,094 admissions of diabetics to the Joslin Cl
service at the New England Deaconess Hospital in the ten years from 1
through 1950, there were only 38 separate cases of acute hepatitis In

ler[37] reported 63 cases of hepatitis occurring among diabetic patients at
Royal Hospital, Sheffield, during a time when there was a high incide
of the disease in the general population

Havens[38] described in some detail the course of two diabetic pati
with acute viral hepatitis, one of whom died He discusses the impac

for children

Cirrhosis of the Liver —The question as to whether cirrhosis of the l
is more common in diabetic patients than in the general population is

[36] Fulde Deut Arch f klin Med, *173*, 404, 1932
[37] Droller Brit Med Jour, *1*, 623, 1945
[38] Havens Med Clin North Am, *39*, 1685, 1955

first were noticed. Both gastric and duodenal ulcers were found in three instances by *x*-ray. Surgical specimens revealed an additional 5 cases with both gastric and duodenal ulcers. Fifty-nine patients had diabetes for varying periods of time before the onset of ulcer symptoms and the remaining 35 patients had peptic ulcer first and developed diabetes later. A striking feature of the series was the fact that in 50 patients typical ulcer pain with respect to severity, relationship to food and localization of pain was lacking. Gastric acidity was determined in 58 cases. In 21, no free hydrochloric acid was obtained in the first specimen and in 18 cases the value was under 20 degrees. Five patients showed no free hydrochloric acid even after the injection of histamine. The development of severe ulcer complications was unusually frequent and occurred at an average age of 61.6 years when the ulcer had been present an average of 6.0 years. Thus 54 individuals developed either massive hemorrhage, obstruction, perforation or gastric carcinoma. Gross or massive hemorrhage occurred in 24 cases, in 2 of which it was fatal. Generalized arteriosclerosis was recognized in 42 patients not merely from palpation of the radial arteries but by study of the heart, kidney function and cerebral symptoms. Undoubtedly the age of the patient and the presence of generalized arteriosclerosis in the vessels supplying the region of the ulcer is an important factor in the frequency of severe hemorrhage. Perforation occurred in 10 cases or 10.6 per cent of the series. Gastric obstruction and retention was the largest single serious complication. In 32 cases or 34 per cent of all the diabetics with ulcers, obstruction was demonstrated by *x*-ray or operation. Five of these cases required a subtotal gastrectomy and 1 a posterior gastroenterostomy. Major operations were performed in 13 cases among the whole series of 94 cases. Five deaths occurred in the hospital, 2 from acute hemorrhage, 1 with an acute perforation and peritonitis and 2 postoperatively from embolism and from peritonitis.

Treatment. Treatment of peptic ulcer in diabetics follows the same [illegible]

the relative amounts of these liquids may be adjusted so as to provide, from a diabetic standpoint, a satisfactory amount of carbohydrate, protein and fat. Strict adherence to the program of rest, frequent bland feedings, antacids, antispasmodics, and control of hyperglycemia and glycosuria are essential.

E. DIVERTICULA OF THE DUODENUM

Cases 3782 and 13253 were found on roentgen-ray examination to have diverticula of the duodenum and have been reported by Thorning and Root.[35] Since then 43 more cases were recorded through 1957, and the list is certainly not complete. The 2 published cases had had previous operations for gall stones and Case 13253, had a nodular enlargement of the liver due presumably to metastatic carcinoma. The possibility that inflammation in

[35] Thorning and Root: Am. Jour. Digest. Dis. and Nutrition, 2, 17, 1935.

Hospital and required at intervals abdominal tapping to relieve ascites At the beginning he had undoubted diabetes, but as the years went on and the process in the liver developed, the diabetes became milder and milder and finally could not be demonstrated by sugar-tolerance tests A somewhat similar case in an elderly man was described by Strieck[45] while working in Grafe's Clinic in Wurzburg and another discussed in the Cabot Case Series of the Massachusetts General Hospital [46] The last-named patient died with multiple abscesses of the kidneys

Enlargement of the Liver.—A common clinical impression is that hepatomegaly is more frequently encountered in diabetics than in a comparable group of non-diabetics However, when one studies actual weights at autopsy, one finds that although there is a trend toward heavier livers in the diabetic patients, this is not striking.[47]

It is true that prior to the introduction of the depot insulins, hepatomegaly was one of the outstanding complications of juvenile diabetes Sixty cases, occurring among 1,077 children, were reported from the Joslin Clinic in 1938 [48] Similar cases have been described by Hanssen[49] and by Mauriac [50] Our patients all had severe, poorly controlled diabetes and approximately one-third of them were true diabetic dwarfs The enlargement of the liver was well-marked, with the lower edge of the organ to be found not infrequently in the pelvis An enlarged spleen was noted in 31 cases The abdomen was usually enlarged to gross inspection and bouts of abdominal pain were common To abdominal palpation the edge of the liver was soft or rapidly became soft and difficult to palpate when the diabetes had been brought under control Moderate hypercholesterinemia was the rule, little or no decrease in the percentage of combined (ester) cholesterol was present Because of Best's[51] work with animals, we treated these patients with betaine over periods as long as eight months but without added benefit of striking degree, although in 50 per cent of cases there was a gradual diminution in size However, with good control of the diabetic condition, made possible by protamine zinc insulin, decrease in the size of the liver occurred in 79 per cent of cases

We have assumed that the enlargement of the liver in these children with poorly controlled diabetes is due primarily to gross fatty infiltration [52] The condition certainly should be regarded as distinct from glycogen storage

biopsy of an enlarged liver revealed not only 10 15 per cent fat but also 12 1 per cent glycogen In the patient of Stetson and Ohler,[53] a twelve year old

[45] Strieck Deut Arch f klin Med, *178*, 167, 1935
[46] Kranes, Jones, Root, and Mallory New England Jour Med, *214*, 1314, 1936
[47] Warren and LeCompte Loc cit, p 170
[48] Marble, White, Bogan and Smith Arch Int Med, *62*, 740, 1938
[49] Hanssen Jour Am Med Assn, *106*, 914, 1936
[50] Mauriac Paris Med, *2*, 525, 1931
[51] Best Lancet, *1*, 1274, 1934
[52] White, Marble, Bogan and Smith Arch Int Med, *62*, 751, 1938
[53] Stetson and Ohler New England Jour Med, *217*, 627, 1937.

ficult to answer. In our own experience, it has not been a common complication and it has been our impression that there is no significant difference between the incidence of portal cirrhosis in diabetics and nondiabetics. In the ten-year period from 1941 through 1950, among 20,094 diabetic admissions to the Joslin Clinic service at the New England Deaconess Hospital there were 88 separate cases of cirrhosis of the liver, an average of 8.8 cases each year, or an incidence of 0.44 per cent. Among 18,439 admissions of diabetes during the seven years from 1951 through 1957, the diagnosis of cirrhosis of the liver was made in 144 or 0.78 per cent. Others have likewise reported a low incidence of cirrhosis among diabetics. Wilder[39] noted evidence of cirrhosis or of hepatitis in only 17 or 0.7 per cent of 2584 diabetic patients at the Mayo Clinic in 1935 to 1937. Frankel, Asbury and Baker[40] found 36 cases of cirrhosis in 3,543 diabetics, an incidence of 1.2 per cent.

On the other hand, data from post-mortem examinations suggest a much more frequent coexistence of diabetes and cirrhosis. Schleusner,[41] of the Barmbeck General Hospital in Hamburg, analyzed 355 autopsy protocols of diabetic patients dying between the years 1930 and 1936. Among these there were 45 patients, 24 men and 21 women, who showed macroscopic evidence of cirrhosis of the liver, making an extraordinarily high incidence of 12.7 per cent. Schleusner concedes that in only one-third of the cases was the cirrhosis so outspoken that it could be diagnosed clinically. He was able to study carefully the histories of 20 of the 45 cases, in all instances the onset of diabetes seemed to antedate that of cirrhosis of the liver. Jaques[42] reported that postmortem examination of 177 diabetic patients dying at the Peter Bent Brigham Hospital in Boston from 1928 to 1950, revealed portal cirrhosis in 16.3 per cent in contrast to an incidence of 8.4

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genic function of the liver. Rarely, however, the influence of the cirrhosis may be the exact opposite as in the case reported by Bordley.[43] This patient, a sea captain, was studied over a period of years at the Johns Hopkins

[39] Wilder, P. 309, loc. cit., p. 71.

falein retention (6 to 13 per cent of the dye still present after 45 minutes) was the only abnormality in 9 patients. With the exception of 1 patient with a bromsulfalein retention of 6 per cent, 15 patients with diabetes of more than twenty years' duration had entirely normal liver function tests.

The paper of Bradley and co-workers should be consulted for a summary [illegible]

patients with diabetes, 7 with portal cirrhosis but no diabetes, and 10 with liver diseases other than cirrhosis. Among some of the diabetic patients, abnormalities of serum protein and bromsulfalein retention were noted frequently whereas abnormal turbidity and flocculation tests occurred infrequently.

In summary, consideration of data both from the literature and from our own experience leads us to conclude that in a patient with well-controlled diabetes, who is of standard weight, who is receiving a completely adequate diet and who is free from complications which apart from diabetes might affect liver function, one may anticipate that the results of liver function tests will agree closely with those of a control group of non-diabetic individuals. However, insofar as the group chosen deviates from such conditions of study, just so far may one find abnormalities. The importance in any study of carrying out similar tests in a comparable non-diabetic control group must not be overlooked.

I. HEMOCHROMATOSIS

Incidence.—Hemochromatosis with diabetes is an uncommon disease. When She[illegible]
search of [illegible]
cluded 34 [illegible]
recognized but one case among 4491 diabetic patients. Only 30 cases were observed at the Mayo Clinic in fifteen years.[62] Our own experience[63] included, up to January, 1951, 30 proven cases of hemochromatosis among approximately 30,000 new cases of diabetes seen in this clinic since 1922, thus representing an incidence of about 0.10 per cent.

Among approximately 20,000 additional patients with diabetes seen from 1951 through 1958 there were 12 other cases of hemochromatosis. Consequently of about 50,000 diabetic patients, 42 or 0.08 per cent were shown to have hemochromatosis. It is reasonable to state, therefore, that in our experience somewhat less than 1 of 1000 patients with diabetes has hemochromatosis.[63a]

[illegible] 955

[illegible] Am. Jour. Med., 11, 500, 1951.

[63a] Marble and Steinke: Die Medizinische. To be published.

Warren and LeCompte[54] emphasize the importance of the fluid content of the liver and state that on histological examination some of the larger livers exhibit hydrops of the cells rather than excess of fat or glycogen.

Liver Function in Diabetes.—Ever since the general availability of various tests of liver function, there has been much disagreement as to the incidence of impairment of hepatic function among persons with diabetes. Various workers (cited by Bradley *et al.*[56]) have reported that abnormal findings may be found frequently in diabetics to the extent of 26 to 71 per cent of those studied. Others[55,56,57] have published findings which show little or no difference from those obtained in groups of comparable non-diabetic individuals. At the outset it may be stated that the difference in results obtained by various workers would appear to be related to the types of patients studied. Because of the confusion created by diverse findings, the matter was studied anew in our patients by Bradley, Sagild and Schertenleib.[56] They carried out a series of liver function tests in 118 diabetic patients, aged fourteen to seventy-seven years (averaging forty-three years), with no unrelated liver disease, acute illness or marked degree of poor diabetic control. The liver function tests performed were thymol turbidity, thymol flocculation, cephalin cholesterol flocculation, one minute prompt direct-acting bilirubin, total bilirubin and bromsulfalein retention. Standards for comparison were based on results obtained on a comparable group of non-diabetic patients. Their findings are summarized in Table 82.

TABLE 82. RESULTS OF LIVER FUNCTION TESTS IN 118 PATIENTS WITH DIABETES
(From Bradley, Sagild and Schertenleib[56])

Procedure	*No. of Patients Tested*	*Borderline Test*		*Positive Test*		*Test Both Borderline & Positive*	
		No.	*Per Cent*	*No.*	*Per Cent*	*No.*	*Per Cent*
Thymol turbidity	118	2	1.7	1	0.8	3	2.5
Thymol flocculation	118	2	1.7	1	0.8	3	2.5
Cephalin flocculation	118	9	7.6	3	2.5	12	10.0
Serum bilirubin							
Prompt direct	117	0	0	1	0.8	1	0.8
Total	117	0	0	8	6.8	8	6.8
Bromsulfalein retention	111	0	0	12	10.8	12	10.8

An analysis of the data of Bradley *et al.* shows that a total of 16 persons (14.4 per cent) gave abnormal findings on the basis of one or more tests and only 6 (5.4 per cent) by two or more tests. A slight increase in bromsul-

[illegible] d., 253, 454, 1955

[56] Bradley *et al.* [illegible]

falein retention (6 to 13 per cent of the dye still present after 45 minutes) was the only abnormality in 9 patients. With the exception of 1 patient with a bromsulfalein retention of 6 per cent, 15 patients with diabetes of more than twenty years' duration had entirely normal liver function tests

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In summary, consideration of data both from the literature and from our own experience leads us to conclude that in a patient with well-controlled diabetes, who is of standard weight, who is receiving a completely adequate diet and who is free from complications which apart from diabetes might affect liver function, one may anticipate that the results of liver

control group must not be overlooked

I HEMOCHROMATOSIS

Incidence.—Hemochromatosis with diabetes is an uncommon disease. When Sheldon[60] wrote his monograph on the subject in 1935, an exhaustive search of the world literature revealed only 345 cases and of these he ex-

included, up to January, 1951, 30 proven cases of hemochromatosis among approximately 30,000 new cases of diabetes seen in this clinic since 1922, thus representing an incidence of about 0 10 per cent

Among approximately 20,000 additional patients with diabetes seen from 1951 through 1958 there were 12 other cases of hemochromatosis. Consequently of about 50,000 diabetic patients, 42 or 0 08 per cent were shown to have hemochromatosis It is reasonable to state, therefore, that in our

Etiology.—*In recent years the mechanism of production of hemochroma-*

to the 2 or 3 grams normally found. Hemochromatosis appears to be an "inborn error of metabolism" characterized by an abnormal degree of absorption of iron from the gastro-intestinal tract. It is considered that normally there exists a "mucosal block" which prevents absorption from the gastro-intestinal tract of iron for which there is no need. In hemochromatosis this natural barrier is not effective and abnormal amounts of iron are absorbed.[64] A second important consideration is the fact that once *iron gains admission to the body proper, there is no normal avenue for* excretion of significant amounts. The quantities found in the urine or excreted into the bowel are very small. Thus according to current concepts iron absorbed into the body proper is trapped; it is used over and over and not excreted to any significant degree. *In hemochromatosis accumulation* of small amounts continues over years of time and it is usually not until the *age of forty to fifty years that sufficient iron has been deposited in important* viscera and sufficient secondary changes set up to cause impairment of function with attendant signs and symptoms.[65] As noted above, the deposition of iron occurs throughout the body but the regions in which changes become most manifest clinically are (*a*) the liver in which cirrhosis occurs, (*b*) the pancreas in which cellular damage and fibrosis may impair insulin function with the production of diabetes, (*c*) the skin in which the presence of iron pigment along with increased amounts of melanin causes abnormal pigmentation varying from a dirty gray to a bronze color. Thus is set up the triad long regarded as characteristic of hemochromatosis: cirrhosis of the liver, diabetes, and pigmentation of the skin. One should

emochromatosis may be sus-

diagnosis depends upon the finding of hemosiderin in tissues obtained at skin biopsy, liver biopsy, bone marrow aspiration or autopsy. Of these procedures, liver biopsy gives the most definitive and trustworthy findings and skin biopsy is the least satisfactory. Three other procedures have been advocated, namely, (1) examination of the urinary sediment for intracellular hemosiderin, (2) the injection of acidified potassium ferrocyanide intradermally as suggested by Fishback,[66] and (3) the demonstration of an abnormally high serum iron with a high percentage saturation of the iron-binding protein.[67]

Aside from the examination of multiple tissues at postmortem the most conclusive procedure is study of material removed at liver biopsy. However, this is oft

reliable methoc

iron deposits

64 Finch: Jour. Clin. Invest., *28*, 780, 1949.
65 Johnston: Jour. Amer. Diabetes Assn., *19*, 838, 1943.
66 Fishback: Jour. Lab. and Clin. Med., *27*, 98, 1939.
67 Rath and Finch: Jour. Clin. Investigation, *28*, 79, 1949.

imbedded in celloidin, sectioned and stained for iron with potassium ferrocyanide by Mallory's method and counterstained with basic fuchsin. The presence of hemosiderin may be demonstrated in the corium especially in the cells of the sweat glands, in the connective tissue cells and the endothelium of the capillaries and smaller blood vessels The epidermis in some cases may show deposits of hemosiderin in the cells of the basal layers

be helpful in diagnosis The method is as follows:

Less satisfactory in our limited experience has been the intradermal test suggested by Fishback. In fact, in certain cases of proven hemochromatosis the intradermal test has been negative. Furthermore, in one patient a slightly deeper injection (into the corium) was likewise negative

A mixture is made of equal parts of N/100 hydrochloric acid and 0 5 per cent potassium ferrocyanide Of this, 0 1 cc is injected intradermally If significant amounts of iron are present, a deep blue color appears at the site of injection almost immediately The mixture should be handled aseptically but cannot be sterilized by heat

Rath and Finch[67] found that the serum iron averaged 224 gamma per 100 cc in 9 cases of hemochromatosis as compared with a control value in normal individuals of 100 gamma per 100 cc Furthermore, although the

hemochromatosis the serum iron is elevated and, although the iron binding capacity of the plasma protein is less than normal, this capacity is almost completely filled Experience to date indicates that these determinations are of distinct value in the diagnosis of hemochromatosis. It is of interest that qualitatively similar results have been noted in certain apparently healthy relatives of patients with hemochromatosis

Sosman and associates[68] at the Peter Bent Brigham Hospital in Boston detected on an abdominal *x*-ray film an increase in liver density and a double contour line along the diaphragmatic border in a patient later proved to have hemochromatosis Following this, in a review of films of 11 patients with hemochromatosis, they found an increase in liver density in 9 of 10 patients on whom roentgenograms of the abdomen had been taken However, this proposed diagnostic aid has not won general acceptance.

[66] Rous Jour Exper, 28, 645, 1918

[68] Gowdy, Riemanschneider, Dealy and Sosman Not yet published

Etiology.—In recent years the mechanism of production of hemochromatosis has become clearer. It has long been known as a condition in which there was abnormal accumulation of iron in the body. This is a generalized process affecting al

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to the 2 or 3 gram

"inborn error of metabolism" characterized by an abnormal degree of absorption of iron from the gastro-intestinal tract. It is considered that normally there exists a "mucosal block" which prevents absorption from the gastro-intestinal tract of iron for which there is no need. In hemochromatosis this natural barrier is not effective and abnormal amounts of *iron are absorbed.*[64] *A second important consideration is the fact that once* iron gains admission to the body proper, there is no normal avenue for excretion of significant amounts. The quantities found in the urine or excreted into the bowel are very small. Thus according to current concepts iron absorbed into the body proper is trapped; it is used over and over and not excreted to any significant degree. In hemochromatosis accumulation of small amounts continues over years of time and it is usually not until the age of forty to fifty years that sufficient iron has been deposited in important viscera and sufficient secondary changes set up to cause impairment of function with attendant signs and symptoms.[65] As noted above, the deposition of iron occurs throughout the body but the regions in which

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emochromatosis may be sus-

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Aside from the examination of multiple tissues at postmortem the most conclusive procedure is study of material removed at liver biopsy. How-

[64] Finch. Jour Clin Invest, *28*, 780, 1949
[65] Johnston. Jour Amer Diabetes Assn, *19*, 838, 1943
[66] Fishback. Jour Lab and Clin Med, *25*, 98, 1939
[67] Rath and Finch. Jour Clin Investigation, *28*, 79, 1949

The causes of death in the 27 fatal cases were recorded as follows: pneumonia 4, diabetic coma 1, cardiac 6, rupture of esophageal varices 1, peritonitis 1, cancer of the liver 3, and "hemochromatosis" 11. With the occurrence of 3 cases of primary cancer of the liver among the 15 patients in whom an autopsy was carried out, one finds confirmation of the experience of others

Treatment.—With the introduction of insulin in 1922 and with the development in recent years of more satisfactory methods of the treatment of cirrhosis of the liver, the outlook for the patient with hemochromatosis has improved correspondingly. Furthermore, present-day availability of

[illegible]

be supplemented with large amounts of vitamin B complex. It is important that the diet be carefully planned and followed and that the diabetic condition be kept under excellent control Insulin in dosage to maintain

[illegible]

If ascites appears it should be treated with the usual measures If success does not follow the use of a minimal sodium diet and mercurial diuretics, recourse to paracentesis may be necessary

Because of the huge excess of iron already in the body treatment with iron should be avoided even though anemia may be present

In our series 9 patients, 4 in the proven and 5 in the probable group, received testosterone because of evidence of gonadal hypoplasia In at

[illegible]

up by the implantation of pellets of testosterone subcutaneously

A logical method of treating hemochromatosis would be one designed to remove the excess iron from the body Such was attempted some years ago by Balfour and associates[73] using repeated phlebotomies Their patient proved not to be a suitable subject because of an unsuspected hepatoma The matter was taken up anew several years later by Finch and associates[74, 75] In the last [illegible]

with a siz [illegible]

siderable [illegible]

can in a year remove 10 to 13 gm of iron from the body In the average patient about two years of weekly bleeding are necessary to deplete iron

[73] Balfour, Hahn, Bale, Pommerenke and Whipple Jour Exper Med, 76 15, 1942
[74] Finch, Haskins and Finch Jour Clin Invest, 29, 1078, 1950
[75] Finch and Finch Medicine, 34, 381, 1955
[76] Gitlow and Beyers Jour Lab and Clin Med, 39, 337, 1952
[77] Warthin, Peterson and Barr Ann Int Med, 38, 1066, 1953
[78] Davis and Arrowsmith Jour Lab and Clin Med, 39, 526, 1952

Clinical Features.—Of our 30 proven cases of hemochromatosis reported in 1951, 3 were females. The rarity of hemochromatosis among women is well recognized; Sheldon[70] found only 13 cases among a total of 311 cases in the literature. It is possible that the infrequency in women may be related to the periodic loss of menstrual blood. Among the 30 cases the age at onset of diabetes varied from 36.7 to 78.1 years. Because the onset of symptoms was so indefinite, the date of onset of hemochromatosis could not be established. Two of the 30 patients, Cases 22158 and 28576, were living with a duration of diabetes to January, 1951, of 8.8 and 13.0 years, respectively. Case 22158 has since died; the duration of diabetes at death was 14.3 years. The other patient, a woman aged 77.2 years, was still living in September, 1958 after more than 20 years of diabetes, despite crippling arthritis and chronic pyelonephritis. Among the fatal cases originally reported, the average age at death was 57.8 years and the duration of diabetes 4.9 years. One of the most extraordinary patients was Case 12069, a man in whom the diagnosis of hemochromatosis was made at the time of onset of diabetes at the age of forty-five.[71] He lived for seventeen years, dying at the age of sixty-two with carcinoma of the liver.

The severity of diabetes as judged by the insulin requirement varied considerably from patient to patient. The average was somewhat greater than that of most diabetic patients, being 62 units per day as a maximum dose. Six patients at one time or another received 100 or more units daily. Outstanding in his insulin requirement was Case 6247, a physician, who died in diabetic coma in 1927 in his home, despite the fact that a physician [illegible] -ior to death.[72] It [illegible] was no abnormal [illegible] de until the post-mortem examination.

In 12 of the 30 cases there was a family history of diabetes but in no instance was there a history of hemochromatosis in relatives. As regards alcohol intake, 16 of the 30 patients were total abstainers and only 7 had taken moderate amounts of alcohol.

The symptoms and signs among the 30 cases included (*a*) a weakness and loss of weight in all cases, (*b*) abnormal pigmentation of the skin in [illegible]

[illegible] not so studied and hence no statement regarding incidence is possible. However, in males with hemochromatosis seen in recent years impotence and loss of libido were frequent complaints. Correlated with this was the frequent finding of thinning and loss of axillary and pubic hair, softening and atrophy of the testes and marked diminution in the size of the prostate.

The decreased excretion of 17-ketosteroids in the urine found in each of 6 patients in whom determinations were made may have been due in part to gonadal hypoplasia and in part to diminished liver function.

[70] Sheldon: Loc. cit., p. 173.
[71] Marble and Smith: Jour. Lab. and Clin. Med., *12*, 1592, 1939.
[72] Root: New England Jour. Med., *201*, 201, 1929.

diabetics in the same age group Thus the incidence of gall stones alone was 30.7 per cent in the diabetic as compared with 21 4 per cent in the non-diabetic group. In 197 autopsies on diabetic patients at the Mayo Clinic between 1919 and 1936, gall stones either were present or had been removed at an operation in 66 or 33 5 per cent of the cases [91]

Although approximately 1 in 4 diabetic patients is found to have gall stones at autopsy, by no means are all the cases recognized during life In 1928, 5400 cases, including 4003 true diabetics over twenty years of age, were studied with this point in mind Data were compiled from clinical histories, surgical operations and autopsies. One hundred ninety-nine *cases, or 5 per cent, were found in 4589 cases of true diabetes* Forty of the patients were males and 159, females. The average age at diagnosis of cholelithiasis in 189 cases was 47 7 years and of the diabetes in 199 cases was 51 3 years, thus showing a definite but not marked precedence of gall stones. However, in Case 10646, our youngest patient to be operated upon for removal of gall-stones, surgery was carried out eighteen months after the onset of diabetes which occurred at thirteen years of age.

Gall-bladder disease has not been prominent as the chief cause of death in our patients Of 18,055 deaths from 1922 to 1957, only 76, or 0 4 per cent, were ascribed by the attending physician to gall-bladder disease

Among 48 unselected cases of diabetes at the Massachusetts General and New England Deaconess Hospitals, Jones and co-workers[92] found cholelithiasis, as diagnosed by examination of the duodenal sediment, in 19 per cent In addition, several other patients had histories or operative findings consistent with the diagnosis of gall stones

According to Rabinowitch,[93] 80 per cent of patients with symptoms of cholelithiasis showed hyperglycemia, *though not of sufficient degree to* produce glycosuria He found at the Montreal General Hospital that "nine times as many patients with dise

diabetes as would be expected

independent The inciden

than in cholelithiasis and that in acute pancreatitis the incidence was forty times greater than chance would allow " With cholecystograms Tedstrom *et al* [94] showed that 44 per cent of 70 diabetic patients past the age of forty years had abnormalities in the gall-bladder The percentage in males was 24 and in females 49 Ophuls[95] found pancreatic lesions associated with gall stones at 14 of 214 autopsies The lesions consisted of focal necroses, chronic pancreatitis, and acute hemorrhagic pancreatitis

Schleusner[96] cites the following from the literature Singer[97] found 61 cases of gall-bladder or liver disease among 450 diabetics. Ferger[98] *found* gall-bladder histories in 19 4 per cent of a series of 100 diabetic patients and in 16, or 10 per cent of the total, he believed there was a definite con-

[91] Wilder P 311 loc cit p 71
[92] Jones Castle Mulholland and Bailey loc cit, p 466
[93] Rabinowitch Canad Med Assn Jour *14*, 296, 1924
[94] Tedstrom Bond, Olmsted and Moore Jour Am Med Assn, 87, 1603 1926
[95] Ophuls Stanford Univ Pub *1*, 131, 1926
[96] Schleusner loc cit, p 470
[97] Singer Ztschr f klin Med, *114*, 497, 1930 Med Klin, *24*, 1858, 1928
[98] Ferger Ibid, *119*, 81, 1931

stores sufficiently. After that, the frequency of venesection may be lessened to once in two or three weeks and later to once in one to three months. Serial needle biopsies of the liver reflect the decrease in the abnormally large iron stores and tests may show the expected improvement in liver function. Clinical improvement may keep pace with this. It is evident that repeated venesections should not be carried out on patients who, because of renal or other disease, are unable to regenerate blood satisfactorily despite an overabundance of iron in the body.

We have treated six patients by means of repeated venesection. The results have been encouraging. Case 40362 has had 85 liters of blood removed during the last seven years. In this patient the liver and spleen appear definitely smaller.[78]

The problem of pigmentary cirrhosis has been approached from a different angle by Bell.[79] He studied tissues obtained at 932 autopsies on individuals with whom the diagnosis of portal cirrhosis had been made clinically. Microscopic sections of the liver were stained for iron in 733 cases. The amount of iron varied from a trace to massive quantities. Some degree of hemosiderosis of the liver was found in 34.2 per cent of 506 males and 23 per cent of 226 females. Bell noted all stages of involvement between full-blown hemochromatosis and nonpigmentary cirrhosis and concluded that pigmentary cirrhosis is not a sharply defined entity. Table 83,

TABLE 83.—RELATION OF DIABETES TO THE DEGREE OF HEMOSIDEROSIS OF THE LIVER

Degree of hemosiderosis	*No. of cases of cirrhosis*	*No. of diabetics*	*Per Cent diabetic*
Nonpigmentary cirrhosis	333	35	10.5
Grade 1 –	22	0	0.0
Grade 1	57	5	8.8
Grade 2	52	8	15.4
Grade 3	40	16	40.0

taken from his paper, indicates the much greater incidence of diabetes

J. GALL STONES AND GALL-BLADDER DISEASE

Incidence of Gall Stones Among Diabetics.—That disease of the gall-bladder is more common in the diabetic than in the general population seems definitely established. Warr
139, and cholecystitis without stone
of age as contrasted with 107 and

[78] Marble and Steinke. Loc. cit., p. 473.
[79] Bell: Diabetes, 4, 435, 1955.
[80] Warren and LeCompte: P. 107, Loc. cit., p. 170.

Insurance Company were also able to demonstrate little or no connection between gall-bladder disease and the development of diabetes They studied the records of 2720 applicants accepted for insurance during the years 1912 to 1928 and traced to their policy anniversary in 1933 There were 150 deaths in the group Despite the inclusion of a large number of females of more than average weight there were no deaths from diabetes among them and only three among males

Dr William R. Jordan,[100] formerly of our group, studied the records of 154 patients with diabetes (including 3 who had glycosuria not proven [illegible] n of

[illegible] dia-

[illegible]

of diabetes.

5 [illegible]

[illegible] sequent observations and treatment in postoperative gall-bladder cases over a long period of years

6 Gall-bladder drainage or removal did not cause improvement of the diabetes as compared with a control group with gall-bladder disease and no operation The only obvious exceptions occurred in patients with prolonged or frequently recurrent acute or subacute inflammation of the gall-bladder, and this is in accordance with the improvement of diabetes following the treatment of any active infection such as a carbuncle

In summary, it seems fair to conclude that although cholelithiasis and cholecystitis occur more frequently in diabetics than in non-diabetics, gall-bladder disease cannot be regarded as a primary factor in the causation of diabetes

Surgery in Gall-bladder Disease — Eusele[101] analyzed the findings in [illegible]

[100] Jordan Unpublished data.
[101] Eusele Ann Surg, *118*, 107, 1943

nection between disease of the gall-bladder and the appearance of diabetes. Lande[89] found histories of gall-bladder disease in 219, or 9.6 per cent, of 2100 cases. Schleusner himself analyzed 355 autopsy protocols of diabetic patients dying in the Barmbeck General Hospital in Hamburg between the years 1914 and 1936. In 119 of these patients stones were found and in 6 other patients the gall-bladder had been removed. Consequently, in 35.2 per cent, gall stones had been found or cholecystectomy carried out. Schleusner regards this percentage so great as to demonstrate without question the increased incidence of gall stones in diabetes.

Incidence of Gall Stones Among Non-diabetics.—Published reports as to the occurrence of gall stones among the general population vary so widely that accurate comparison of diabetic and non-diabetic groups is difficult. At one extreme we have White's[90] statement that in only 3 per cent of 11,031 autopsies at Guy's Hospital were gall stones found, and at the other, Mentzer's[91] finding that in 21 per cent of 600 autopsies at the Mayo Clinic, stones were noted. Kaufmann[92] reported the presence of stones in 10.9 per cent of 16,025 autopsies at Basle. Ophüls[93] found 206 cases, or 8 per cent, among 2492 autopsies performed on patients over twenty years of age. Schleusner[94] quotes Aschoff as finding gall stones 100 to 150 times in 1000 autopsies on non-diabetic individuals.

Relationship Between Gall-bladder Disease and Diabetes.—If we grant that cholelithiasis and cholecystitis are more common in diabetics than non-diabetics, are we justified in assuming an etiological relationship? Katsch[95] stated that diabetes is often the consequence of chronic gall-bladder disease, manifest or silent, and this was a belief commonly held in the past. However, in view of the recent emphasis of the common hereditary basis of diabetes we believe that one can no longer assign to gall-bladder disease a primary etiological rôle.

Terbruggen[96] thought that the occurrence of gall-bladder disease and diabetes in the same individual is explained by the obesity which is so commonly present in such a person. This was the conclusion reached also by Bowen, Vaughan and Koenig.[97]

In a study of 2100 diabetic patients Lande[98] was unable to demonstrate a definite influence of gall-bladder or stomach disease upon the onset of diabetes except in those rare cases in which inflammatory conditions of the biliary system had by extension affected the pancreas and there led to marked involvement of islet tissue. By approaching the problem from the other direction, Dublin, Jimenis and Marks[99] of the Metropolitan Life

[89] Lande. Loc cit, p 467.
[90] White. Clin Jour, *30*, 273, 1907.
[91] Mentzer. Arch Surg, *14*, 14, 1927.
[92] *Kaufmann*. Lehrbuch der Speziellen Pathologischen Anatomie, 8th ed, Berlin, p 779, 1922.
[93] Ophüls. Loc cit, p 479.
[94] Schleusner. Loc cit, p 170.
[95] Katsch ... Deutsch med Wchnschr, *54*, 1508, 1928, J...
[96] Terbrüg...
[97] Bowen, ... ull, *6*, 41, 1928.
[98] Lande. Loc cit, p ...
[99] Dublin, Jimenis, and Marks. Proc Assn Life Ins Med Directors Amer, *21*, 34, 1934.

Chapter 18

THE NERVOUS SYSTEM AND DIABETES

HOWARD F. ROOT, M.D.

General Considerations.—Renewed interest in the neurologic complications of diabetes has yielded new data, directing attention particularly to the autonomic nervous system, to certain of the less frequent clinical features associated with diabetic coma and to the association of neuropathy with diabetic retinitis and nephropathy. The use of more sensitive technical methods makes it clear that careful study will reveal some form of neuropathy in a large per cent of diabetic patients, who have had diabetes more than a few years.

Clinical lesions of the nervous system occurring in diabetic patients in a general hospital population consist chiefly of diabetic neuropathies and cerebral vascular accidents. In Table 84 are summarized diagnoses involving the nervous system in 3174 diabetics treated in the New England Deaconess Hospital between January 1, 1946, and January 1, 1957.

TABLE 84.—DIAGNOSES INVOLVING THE NERVOUS SYSTEM IN 3174 DIABETICS NEW ENGLAND DEACONESS HOSPITAL, JAN. 1, 1946 TO JAN. 1, 1957

[illegible]	2061
[illegible]	39
[illegible]	80
[illegible]	684
[illegible]	12
Paralysis Agitans	50
Acromegaly	3
Epilepsy	93
Cushing's Disease	2
Meningitis	1
Multiple Sclerosis	6
[illegible]	20
[illegible]	2
[illegible]	17
Trigeminal Neuralgia	1
Miscellaneous	103
Total	3174

Under the heading of neuropathy are included 2061 patients in whom the symptoms and findings indicated diabetic neuritis characterized by loss of peripheral reflexes, hyperesthesia, paresthesia, nocturnal pain and in some cases motor involvement, paralysis, and muscular atrophy. Under the same heading have been included such diagnoses as pseudo-Charcot feet, bladder paralysis and ocular palsies. Many cases of partially anes-

illustrated by its occurrence in 8 of 65 patients coming to operation without neoplasm, an incidence of 14 per cent (Cases 6435, 8929, 10803, 12778, 15273 15497, 15910, 17466) Three of the perforations were in acutely inflamed gall-bladders and 3 were in gall-bladders with empyema. The high incidence of gall-bladder perforation is consistent with the well-known fact that the diabetic patient often does not limit infection in a normal manner Commonly quoted statistics in all biliary tract disease indicate a 1 to 3 per cent incidence of perforation, in contrast to the 14 per cent in this series Eradication of the diseased gall-bladder did not influence the severity of the diabetes as measured by the insulin requirement one year before as compared with one year after operation.

Rabinowitch[192] reported upon the operative treatment of chronic gall-bladder disease in 50 diabetics as compared with 179 non-diabetic cases. The mortality in the diabetic group (4 per cent) was less than in the non-diabetic (5.5 per cent). The average age of the diabetic was 51 8 years as compared with 47.2 for the control group.

Abramson[193] reviewed the cases of 25 diabetic patients, 18 females and 7 males, who had had a cholecystectomy. In this series acute inflammation of the gall-bladder occurred in 32 per cent and jaundice in 28 per cent of cases, a much higher incidence than in non-diabetic patients Acute pancreatitis occurred in 2, and chronic pancreatitis in 3 patients. Fatty infiltration of the liver was present in all 3 patients on whom biopsies were carried out From his experience Abramson concluded that improvement of the diabetic state may be expected in most patients subjected to cholecystectomy He believes that this improvement is related not only to the overcoming of infection but also to functional improvement in the liver and pancreas, depending upon the amount of damage to these organs which has occurred

Our own advice both to diabetic and non-diabetic patients with gall stones is to be operated upon when the conditions of time, place, surgeon and physician are propitious Delay and neglect may permit repeated attacks of gall stone colic with the danger of perforation and, in the opinion of certain clinicians, may favor the development of diabetes in the hereditarily predisposed non-diabetic

[192] Rabinowitch Ann Surg, 96, 70, 1932
[193] Abramson Ibid 145, 370, 1957

phasic personality inventory were applied, results indicated clearly that although the diabetics showed some abnormal deviations in terms of rebellious aggression and other tendencies, these differences disappeared entirely when the series was compared to populations comparable in age to the diabetics. Similarly the diabetic intelligence quotients fell in the middle of the normal range. These results confirm the impression that, although some diabetic patients have shown superiority in mental achievement, on the whole, diabetic patients do not present any greater personality problems or other deviations than non-diabetic patients of similar ages.

A. DIABETIC NEUROPATHY

The occurrence of characteristic disorders of the nervous system as a result of diabetes mellitus rather than as a cause of diabetes was first [illegible]

complications involving the nervous system.

Diabetic neuropathy may be defined as an acute or chronic degenerative condition of the peripheral nerves, autonomic nervous system or central nervous system, peculiar to diabetes. It involves chiefly the nerves to the lower extremities and is much more frequent than most reports indicate. Probably the most frequent finding is the impairment of vibratory sensation in the extremities which has been reported to occur in probably 95 per cent of diabetic patients with diabetes uncontrolled for a period of years. In Mirsky's[4] study of 102 cases, he measured vibratory perception by means of an inaudible electromagnetic vibrator. The vibratory perception threshold steadily regressed in all diabetics with increasing age, when measured in either the index finger or the toe. The evidence of neuropathy by this method as well as the usual clinical evidences, rose from 80 per cent of patients between 21 and 30 years to 100 per cent in those between the ages of 71 and 8[illegible]

tion were c[illegible]

for periods [illegible]

demonstration of curves approaching normal or receding from normal with the improvement or activation of the diabetic status.

In Mirsky's[4] series, the impairment of vibration sense increased with age at about the same rate as was true in non-diabetic patients. At every age, however, the degree of impairment in vibratory sense of diabetic patients placed them in a separate category from the non-diabetic patients.

Diabetic neuropathy may manifest itself in many ways. Where neuropathy occurs in patients over fifty years of age with relatively mild diabetes, paresthesiae, night pain, loss of deep reflexes and impaired sensation, as

[1] deCalvi. Recherches sur les accidents diabétique, Paris, P. Asselin, 1864.
[2] Mirsky. Proc. Assn. Res. Nerv. and Ment. Dis., 42, 328, 1950.
[3] Barach. Diabetes and Its Treatment. New York: Oxford University Press, p. 125, 1949.
[4] Collens, Boas and Slinsky. Amer. Jour. Med. Sci., 219, 482, 1952.
[5] Mirsky. Loc. cit. p. 485. Lundbaek. Acta Med. Scand., 158, 447, 1957.

thetic feet associated with surgical infections or gangrene have escaped inclusion. Diabetic diarrhea occurred in 119 cases, associated with other neuropathy in 39 cases. The 93 cases of epilepsy represent a special group in which diabetes may be a contributing factor in the sense that repeated insulin reactions with hypoglycemia may have uncovered and brought to clinical reality an epilepsy which was latent.

Diabetic neuropathy followed by or associated with retinopathy and nephropathy has been characterized as a malignant triopathy (See Table 86).

Brain tumors (12), paralysis agitans (50), with a variety of isolated and miscellaneous conditions made up a total of 219 cases. Hypoglycemia is discussed in Chapters 10 and 11. Cerebral vascular accidents in 681 patients point to the fact that among 2576 diabetic admissions to the New England Deaconess Hospital in one year, 1805 individuals were over forty years of age, and 315 exceeded seventy years of age. In this older group, it is difficult to estimate the influence of diabetes in the presence of long-standing *hypertension and arteriosclerosis. However, in the large group* of patients whose diabetes began in childhood or youth, the existence of various forms of diabetic neuropathy in association with diabetic retinitis and diabetic nephropathy strongly suggest a common diabetic etiology. The co-existence of diabetic retinal disease with peripheral neuropathy has been noted by many writers. Today, the frequency of neuropathy in association with retinitis and diabetic nephropathy justifies the assumption that diabetic neuropathy is intimately related with the general problem of diabetic degenerative sequelæ dependent upon the long duration of imperfectly controlled diabetes. If this assumption be true, then the association of neuropathies of a severe type, retinitis, and finally diabetic nephropathy may be predicted to occur with greatest frequency among patients with severe diabetes beginning in childhood or before forty years of age, and continuing over a long period of time. Such has been our experience.

The persona [illegible]
jects of many [illegible]
personality or [illegible]
been reported but usually on the basis of clinical observations for only a few cases. Kubany, Danowski and Moses[1] group such studies under four headings:

1. Attempts to show an emotional basis for the onset of diabetes. Such psychoanalytic studies have been few, with conflicting results.
2. Studies relating recurring acidosis to emotional causes.
3. Studies indicating that diabetic patients have a particular personality pattern, differentiating them from normals with particular emphasis upon anxiety, resistance, and even schizoid states.
4. Studies of intelligence *have been difficult to interpret because* of variations in sampling. In the excellent study of Kubany *et al.*, a group of young diabetics from the Children's Hospital in Pittsburgh, together with a group of adults, were compared with a control series of similar age. When the Stanford-Binet tests of intelligence and the Minnesota multi-

[1] Kubany, Danowski and Moses: Diabetes, *5*, 462, 1956.

throughout the night until the discomfort subsides in the early morning hours Thereafter the pain may not recur until the following night No adequate explanation for the nocturnal character of the pain has been advanced

Paresthesias are frequent, occurring in 70 per cent of Jordan's[7] series,

Abnormal neurological signs are usual and may at times be the first or only manifestation of the disorder In Rundles' series of 125 cases he found diminished or absent tendon reflexes the most common neurologic abnormality. The achilles tendon reflex was absent in 101 cases (81 per cent) and greatly diminished in another 15, whereas the patellar reflexes were absent on one or both sides in 70 cases (56 per cent) and greatly diminished in an additional 29 The biceps and triceps reflexes were diminished or absent in one-third of his patients Pronounced muscle tenderness was detected in 46 cases. Decreased skin sensitivity occurred in approximately one-half and 9 patients revealed areas of complete anesthesia The vibratory sense at the ankle was diminished in 37 cases and absent in 20

Muscular paresis and paralysis are frequently observed, and complete foot drop and less frequently wrist drop may develop Rundles reports 10 cases of foot drop and emphasizes that the peroneal nerve is more vulnerable than the tibial, and the ulnar nerve more vulnerable than the radial or median

Postural hypotension and tachycardia are often characteristic findings in diabetic neuropathy Postural hypotension may be suspected in a patient who complains of dizziness or faintness on standing, but it may frequently be found in the absence of such symptoms For this reason, it is desirable that the blood pressure, as a routine be taken with the patient lying, sitting and standing In the normal person, the pressure changes little, or may rise on standing A fall of 20–30 mm or more indicates postural hypotension Presumably this finding indicates involvement of autonomic fibres by the neuritic process

The frequency of diabetic neuropathy in relation to lesions of the feet in diabetes is increasingly recognized Cutaneous neuropathic changes commonly start as blisters about the tips of the toes or near a corn or callosity at points of pressure from ill-fitting shoes Lack of normal sensation leads the patient to ignore the lesion and delay treatment until secondary infection takes place Oakley, Catterall and Martin[a] in a survey of 3788 diabetic patients at King's College Hospital emphasized the fact that although peripheral arterial disease was present in 140 of them, the major factor was the associated neuropathy In addition to the usual type they point to the typical deformity of the toes associated with diabetic neuropathy In this condition the cocked-up position of the toes is that in which

[a] Oakley, Catterall and Martin Brit Med Jour 2, 953 1956

measured by tuning fork, pinprick, or light touch, are common findings At any age acute, severe forms, running a course of many months, with extreme pain, loss of weight, loss of appetite, and paralysis may develop from which practically complete recovery takes place in the course of a few months Another group of patients demonstrates an entirely different course. Chronic progressive neuropathy seen in a considerable number, though not a large percentage, of the diabetes neuropathies, might well be described as a slowly progressive degeneration in the nervous system Case 33335, male, a priest age 31 years, at the onset of diabetes in 1929, first came for treatment June 25, 1946, because of bilateral foot drop and ataxia which had first been noted in 1941, at the age of 43 years. Diabetes had never been well controlled because, although he had been taking insulin, dietary measurement had been inexact and he had been warned not to let the urine become sugar-free for fear of insulin reaction. Blood and spinal fluid tests were negative. Absent knee reflexes, bilateral peroneal palsy and a shuffling gait were apparent. During the next three years progressive severe atrophy of the hypothenar muscles and interossei of both hands appeared. By November 12, 1957, his condition had steadily progressed. He could no longer walk without support Pulsations were absent in the
Urine contained
s. The stiff hands
h pain, muscular
atrophy and loss of elastic fibers in skin

Clinical Course.—Most diabetic patients who develop neuropathy have had antecedent periods, usually of months' or years' duration, of neglected or poorly managed and uncontrolled diabetes This has been universally t
Hospital rep
(50 cases).
noted the high blood sugar level and the frequency of the severe type of diabetes with special propensity for the development of ketosis In the 125 cases of Rundles' series, as well as in the 88 cases of Broch and Klovstad,[10] a strong hereditary background has been noted in some cases In a series of 113 cases occurring during the year 1950 at the New England Deaconess Hospital, 12 only seemed under good control upon admission and in no case could it be said that the neuropathy had begun at a time when diabetes was well controlled. In this series, as in Rundles' series, about a quarter of the patients were under forty years of age. Sixty-five per cent were female The duration of diabetes was less than four years in 17 per cent, between five and nineteen years in 75 per cent, and over twenty years in 8 per cent

The most outstanding symptom of diabetic neuritis is pain which is characteristically worse at night The pain may be superficial or deep, aching, grinding, darting, or lancing Not infrequently sleep is prevented

[7] Jordan Arch Int Med, *57*, 307, 1936
[8] Bailey, in Joslin *et al* Treatment of Diabetes, 8th Ed, Philadelphia, Lea and Febiger, p 568, 1946
[9] Bonkalo Arch Int Med, *85*, 944, 1950
[10] Broch and Klovstad Acta Med Scandinav, *127*, 514, 1947

TABLE 85—NEUROPATHY FOLLOWING DIABETIC COMA

Series No	*Case No*	*Sex*	*Age at Onset D M*	*Age at Onset Neuro*	*Nature of Neuropathy and Date*
1	2568	F	7	36	November, 1950 Coma Polyneuritis, paralyses of arms and facial weakness
2	30477	M	17 7	32	Acidosis April 10, 1947—Acidosis Bilateral paralysis
3	41733	M	52 9	64	December, 1952 Coma Polyneuritis, severe paresthesiae Pain
4	18550	F	11	26	Coma Polyneuritis, muscular paralyses, 1 year for recovery
5	B8299 19893	F	8	19	September, 1947 Coma Polyneuritis and diarrhea Pain in legs
6	9230	M	19	19	100 lbs June, 1930—Coma Shoulder girdle paralysis Recovery complete 8 months
7	41105	F	39	40	June, 1952 Coma Right ankle drop Left wrist drop Polyneuritis
8	43878	F	17	31	1951—Acidosis Right ankle drop Loss of proprioception
9	B1754 6265	F	17	11	March, 1954 Coma Encephalopathy Sp Fl protein 188 Respirator required
10	24070	F	56 0	57	December, 1943—Coma Polyneuritis —legs Bladder paralysis Pain
11	24605	F	23 6	39	CO_2 7—B S 748 February, 1954—Acidosis Bladder paralysis Severe abdominal pain
12	45002	M	44 5	45 5	August, 1954 Acidosis Unrecognized D M 1 year plus transverse myelitis-like picture with paraplegia—Paralysis of urinary bladder B P 40 to 60 systolic Levofed for 2 days Gangrene with slough Comatose 3–4 days Spinal Fluid protein 112 mg%

tion and sudomotor activity did not take place in the patients with diabetic neuropathy Studies of resected sections of the sural nerve indicated that the non-myelinated nerve fibers may be the first to suffer damage from the process responsible for the nervous complications of diabetes Sections of nerves [illegible]

sisting

were di

myelinated, small caliber fibers degenerated more extensively than the

they would be drawn by simultaneous contraction of the long flexors and extensors with a normal balancing force of the intrinsic muscles removed This position of the toes is not necessarily associated with or caused by infection, but is accompanied by the tight plantar fascia and short tendo Achilles of the typical case of tabes dorsalis.

Among the varied syndromes associated with diabetes, one has been called amyotrophy. A series of twelve patients has been presented by Garland,[12] who described a syndrome including weakness and marked wasting of muscles with tendon areflexia, associated with frank diabetes Protein content of the cerebrospinal fluid was normal in some but increased in other patients. The affected muscles showed electromyographic changes of varying character. Some of the cases seemed to result from a myelopathy with changes at the cord level.

The earliest phase in the development of diabetic neuropathy with its diffuse pain, vasomotor disturbances, paraesthesiae, changes in tendon reflex and often alteration in pain sensibility is attributed by Martin[13] to widespread degeneration of non-myelinated nerve fibres The impairment of vasomotor responses and to a limited extent pain conduction due to interruption of the lower sensory neurone predisposes to excessive trauma and lowers tissue resistance

Neuropathy Following Diabetic Coma.—In Table 85 are listed twelve cases in which a severe neuropathy developed during or immediately following diabetic coma.

It is seen that the ages of the patients varied from 19 years to 64 years The type of lesions are chiefly polyneuritis, in which pain was the most important symptom, muscular paralyses were prominent. Case No. 12, required more than a year and a half in the hospital before recovery sufficient for return to his home. Unusual neurologic manifestations in diabetic coma are discussed by Lawrence,[14] and a case reported by Gurling,[15] in which convulsions occurred during diabetic ketosis. The unusual features which Lawrence emphasized were maniacal restlessness and violence in a diabetic boy of sixteen, (2) acute abdominal pain with abdominal rigidity, suggesting a surgical lesion, (3) intense lumbar pain, (4) deepening unconsciousness during treatment and (5) epileptiform convulsions

Autonomic Neuropathy.—As long ago as 1890 Buzzard,[16] Pryce,[17] Auche[18] and others described vasomotor and trophic disturbances, including dependent edema, and changes in sweating which they attributed to involvement of the autonomic fibers of peripheral nerves.

Martin[19] investigated the vasomotor, sudomotor and vascular responses in five normal subjects, five new diabetics without peripheral nerve involvement and twenty patients with diabetic neuropathy. The ages varied from 20 to 70 years It was found that reflex vasoconstriction, vasodil

[12] Garland Ibid, *2*, 1287, 1955
[13] Martin Lancet, *1*, 560, 1953
[14] Lawrence Diabetes, *5*, 484, 1956
[15] Gurling Ibid, 486, 1956
[16] Buzzard Brit Med Jour, *1*, 1419, 1890
[17] Pryce Brain, *16*, 416, 1893
[18] Auche Arch de med exper et d'anat path, *2*, 635, 1890
[19] Martin Loc cit, p 188

ous pericarditis. Degenerative changes in the cauda equina roots and peripheral nerves with slight changes in the posterior columns of the spinal cord were noted.

A patient aged 19 years, notable for the fact that he had at that age the fully developed triopathy, was seen in Denver, Colorado through the courtesy of Dr. E. Paul Sheridan. The diabetes which began at the age of 14 years was under non-medical direction for the first two years. After less than five years of diabetes during which time he had four attacks of ketosis, he had diabetic retinopathy, nephropathy, severe nocturnal diarrhea and postural hypotension.

In Table 86[a] are summarized the basic clinical facts regarding a series of 155 such patients. Sixty-eight patients of the series developed the three features of the triopathy between the ages of 20 and 39 years, 58 patients developed the syndrome between the ages of 40 and 59 years, whereas only 29 patients developed the syndrome after the age of 60. Duration of the diabetes is important. Thus, 88 of the patients with diabetes between 10 and 19 years, were in contrast to only 18 patients with diabetes of less than 10 years duration. Forty-nine patients had had diabetes between 20 and 34 years at the full development of the triopathy. The outstanding feature, however, is the frequency of this condition in the more severe type of diabetes which has its onset early in life and in which diabetic control has been least exact.

TABLE 86. TRIOPATHY OF DIABETES IN 155 PATIENTS (51 FATALITIES)

Age of Triopathy Yr.	Duration of Diabetes 0-9 Yr.	10-19 Yr.	20-34 Yr.	Total Cases
20-39	3	42	23	68
40-59	8	32	18	58
60-75	7	14	8	29
Total	18	88	49	155

In this series of 155 cases, as in Case 10015, the multiplicity of neurologic lesions in the same person is to be stressed. Only twenty-one patients had a single neurologic sign or symptom. Thus thirty-five patients who had the nocturnal diarrhea of diabetes had other evidences of diabetic neuropathy, such as severe nocturnal pain, loss of reflexes or ocular motor paralyses. The same was true of patients with Charcot joints, paralyses of the bladder and cases with marked lesions of the autonomic nervous system. As the neuropathy involved the feet with loss of sensation, resistance to infection was seriously impaired and in 25 per cent of the patients amputations of toes, a portion of a foot or an amputation through the supracondylar region were carried out. Retinitis, present in every case, reached the stage of retinitis proliferans in 63 patients. The retinal lesions in many cases were present even before severe typical neurologic lesions occurred. However, the earlier milder form of neuropathy had been

[a] Root, Pote, and Frehner. Arch. Int. Med., 94, 931, 1954.

larger myelinated ones. Biopsies of the sural nerve by Fagerberg[70] indicated also pathologic changes in the nerves in those patients with neuropathy. He particularly stressed the difference in the history in those patients with neuropathy as against the younger patients without neuropathy. In both groups, however, there was constriction in the vessels with thickening of the walls and a similar response to stains for mucopolysaccharides. Autonomic neuropathy may simulate the effects of sympathectomy. In a study of forty patients by Odel, Roth and Keating[71] a clear presentation of this resemblance is made. In 23 out of 29 patients lack of sweating was charted at various levels. A second finding was that the skin temperature which normally is lower in the legs because of vasoconstriction to conserve body heat was often higher than that in the fingers. Orthostatic hypotension occurred in 16 of 20 cases. Impotence, intestinal and bladder disorders, were other findings in the group. Whether the disturbance was of central or peripheral origin was not entirely clear. However, they considered that the lesion was probably of the sympathetic nervous system, distal to the cord. For the treatment of the symptoms, drugs have been relatively ineffective. Use of leg bandages and abdominal binders proved a practical measure in the management of orthostatic hypotension.

Triopathy.—In patients whose diabetes begins early in life a triad is being recognized with increasing frequency, namely, the sequence in the ... malignant ... 015, male, ... treatment ... blood sugar ... the first four years of his ... His chief ... the past four months. During the next five years he did not follow the advised dietary regimen at home, although he took insulin regularly. About 1934 the legs became weak, heavy, the muscles tender, knee reflexes disappeared. ... rafting ... onstipa- ... ys at a time. Soon the diarrhea became nocturnal with an average three to five stools at night. Incontinence was present. Gastro-intestinal *x*-rays were ... it ... t

In 1944 retinal hemorrhages developed and by 1946 he had had a large vitreous hemorrhage in the right and typical retinitis proliferans in the left eye. Albuminuria and hypertension developed in 1946. By 1948 excessive albuminuria and nitrogen retention were present, the insulin dose had fallen from 70 units to 35 units daily. He died in uremia June 1, 1951. Post-mortem examination showed typical diabetic nephropathy with the Kimmelstiel-Wilson lesions, intercapillary glomerulosclerosis, arteriolonephrosclerosis, generalized arteriosclerosis, and atherosclerosis and fibrin-

[70] Fagerberg: Acta Med. Scand., *154*, 145, 1956.
[71] Odel, Roth, and Keating: Diabetes *4*, 92, 1955.

ous pericarditis. Degenerative changes in the cauda equina roots and peripheral nerves with slight changes in the posterior columns of the spinal cord were noted.

A patient aged 19 years, notable for the fact that he had at that age the fully developed triopathy, was seen in Denver, Colorado through the courtesy of Dr. E. Paul Sheridan. The diabetes which began at the age of 14 years was under non-medical direction for the first two years. After less than five years of diabetes during which time he had four attacks of ketosis, he had diabetic retinopathy, nephropathy, severe nocturnal diarrhea and postural hypotension.

In Table 86[22] are summarized the basic clinical facts regarding a series of 155 such patients. Sixty-eight patients of the series developed the three features of the triopathy between the ages of 20 and 39 years, 58 patients developed the syndrome between the ages of 40 and 59 years, whereas only 29 patients developed the syndrome after the age of 60. Duration of the diabetes is important. Thus, 88 of the patients with diabetes between 10 and 19 years, were in contrast to only 18 patients with diabetes of less than 10 years duration. Forty-nine patients had had diabetes between 20 and 34 years at the full development of the triopathy. The outstanding feature, however, is the frequency of this condition in the more severe type of diabetes which has its onset early in life and in which diabetic control has been least exact.

Table 86. Triopathy of Diabetes in 155 Patients (51 Fatalities)

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In this series of 155 cases, as in Case 10015, the multiplicity of neurologic lesions in the same person is to be stressed. Only twenty-one patients had a single neurologic sign or symptom. Thus thirty-five patients who had the nocturnal diarrhea of diabetes had other evidences of diabetic neuropathy such as severe nocturnal pain, loss of reflexes or ocular motor palsies. The same was true of patients with Charcot joints, paralyses of the bladder and cases with marked lesions of the autonomic nervous system. As the neuropathy involved the feet with loss of sensation, resistance to infection was seriously impaired and in 25 per cent of the patients amputations of toes, a portion of a foot or an amputation through the supracondylar region were carried out. Retinitis, present in every case, reached the stage of retinitis proliferans in 64 patients. The retinal lesions in many cases were present even before severe typical neurologic lesions occurred. However the earlier, milder form of neuropathy had been

[22] Root, Pote and Frehner. Arch. Int. Med., 94:931, 1954.

present. The renal status of the patients varied from the early phase with albuminuria and edema, often accompanied by elevated plasma cholesterol value to the more advanced stage with hypertension and nitrogen retention. The cause of death in the fatal cases was preeminently renal failure. Those few cases where the terminal event was coronary occlusion with infarction of the heart or cerebral hemorrhage, the underlying lesion in existence for months prior to the death, was the nephropathy. Uremia itself was the cause of death in 18 of the 23 deaths in which autopsy was performed. In 51 other deaths, uremia was the cause in 33. In every one of our patients at autopsy typical *globular hyaline masses of renal glomeruli occurred* with marked arteriolarsclerosis involving both afferent and efferent arterioles, and varying degrees of chronic pyelonephritis and atheromatosis of the aorta and the renal and coronary vessels. Similar changes occurred in nine cases of Gilliland's[23] series.

In no case of our group could it be said that the patient had well controlled *diabetes throughout the course of his illness.* Delay in the use of insulin had occurred in 75 cases. Among the patients of this series, diabetic coma of severe type had occurred 93 times.

The pathogenesis of the triopathy may begin with the background of the diabetes itself. The tendency to diabetes is believed to be inherited as a recessive gene. That such an inheritance carries with it a special vulnerability of the central nervous system and the vascular system is an hypothesis which is well supported. Other factors may be found in the maternal environment *in utero*, and particularly those alterations, metabolic in nature, which follow the development of the clinical phase of diabetes. The prevention of the triopathy depends upon earlier diagnosis of diabetes and *more accurate treatment from the outset.*

Spinal Fluid.—The striking and often sole abnormality of the spinal fluid in diabetic neuropathy is the abnormal elevation of spinal fluid protein. A comparison of the spinal fluid findings in 84 patients with diabetic [illegible] syphilis, or mis- [illegible] 24 [illegible] d

examinations for 73 later cases. The highest values obtained in diabetic neuritis were 440 and 435 mg. respectively which values fell in the course of two weeks' treatment to 170 and 260 mg. respectively. It is noteworthy that 72 per cent of all cases of diabetic neuropathy have shown a definite elevation in spinal fluid protein. The absence of cells resembles the findings in Guillain-Barré's syndrome.

The colloidal gold curve in diabetic neuropathy usually shows an elevation of the curve to the left in half the cases and a mid-zone rise in occasional cases. Spinal fluid Hinton tests have been negative in all cases of diabetic neuropathy. In general the severity of the neuropathy tends to parallel the level of the spinal fluid protein and clinical improvement is usually accompanied by a decrease in the spinal fluid protein.

The cellular content, pressure and spinal fluid dynamics are characteristically normal in diabetic neuropathy and the globulin usually increased.

[23] Gilliland: Brit. Med. Jour., *1*, 916, 1951.
[24] Joslin and Root: Trans. Assn. Amer. Phys., *54*, 251, 1939.

The diagnosis of diabetic neuropathy may be difficult if the symptoms and signs are atypical. Usually the involvement of peripheral nerves is bilateral and diffuse, with sensory fibers suffering more damage than motor fibers. The smaller caliber fibers are selectively involved—pain and vibration sense particularly. Autonomic involvement leading to postural hypotension, sweating changes and other visceral defects is characteristic. On the other hand, spinal cord involvement with production of upper motor neuron lesions is not typical of diabetic neuropathy. Care should be taken to exclude other conditions before making a confident diagnosis of diabetic neuropathy. In particular, if the neurological signs suggest a single anatomical site for the lesion it becomes essential to rule out other spinal pathology. Spine x-rays, careful manometric readings during lumbar puncture and, if necessary, myelography should be done to exclude spinal tumor and prolapsed intervertebral disc.

TABLE 87.—PROTEIN CONTENT IN CEREBROSPINAL FLUID IN DIABETES[24]

Protein Content (mg. per 100 cc.)		*Diabetic Neuropathy (per cent)*	*Surgical Infections of Feet (per cent)*	*Syphilis (per cent)*	*Others* (per cent)*
Low to Normal	15–50	28	57	42	58
Moderate	51–70	27	26	17	19
High	71–120	34	17	33	12
	121–440	11	0	8	11
Number of cases		157	53	24	74

* Others included meningo-encephalitis (6), tumors (4), epilepsy (6), cerebral hemorrhage (17), miscellaneous (41).

Classification of Neuropathy.—Attempts to subdivide diabetic patients with pain and other evidences of neuropathy into various groups present many difficulties. Recent studies, notably of Martin, give a pathologic basis and ideally a classification should be based on differences of pathology and etiology. However, the lack of knowledge of pathologic changes occurring in diabetic neuropathy makes this an uncertain procedure.

DeTakats[25] has suggested a grouping of cases of diabetic neuropathy, though this classification is not as comprehensive as the others described. His groups represent four clinical pictures seen in diabetics: (1) the painless foot ulcer, (2) the Charcot joint as seen in diabetic pseudotabes, (3) "irritative nerve lesions" seen with deficient peripheral circulation, (4) ischemic neuropathy of posterior root ganglia. DeTakats describes the use of the histamine flare test in studying some of these groups.

More recently Karnosh[26] has listed the diverse conditions seen in diabetic neuropathy as follows:

[25] deTakats: Proc. Am. Diabetes Assn., 5, 183, 1945.
[26] Karnosh: Cleveland Clinic Quart., 16, 227, 1949.

A. Primary Diabetic Neuropathies
  1. Primary diabetic acroneuropathy
  2. Diabetic radiculopathy
  3. Diabetic pseudotabes
     (a) Bladder
     (b) Joints of foot
B. Diabetic Vascular Disorders
  1. *Ischemic neuropathy*
  2. Diabetic ischemic disease of the central nervous system
C. Autonomic Dysfunctions
  1. Loss of pilomotor control
  2. Sweating deficiencies
  3.
  4.
  5.

     (b) Constipation
  6. Sexual impotence
  7. Diabetic edema

This grouping has the advantage of being comprehensive. However, many severe cases of diabetic neuropathy will frequently overlap several of the headings given

Cranial Nerve Paralysis.—Bilateral facial paralysis occurred in Case 9876 during diabetic coma. Facial paralysis is the commonest of the cranial nerve lesions. Case 19678, admitted to the hospital, developed successive bilateral external rectus paralysis within two days. Spinal anesthesia had been used, however, at the time of a transmetatarsal amputation of an infected foot twelve days before the first ocular palsy. In 5 cases of cranial nerve paralysis reported by Root[27] a double paralysis of each internal rectus muscle occurred in 1, the third nerve was involved in 2 cases and the sixth nerve was involved in 2 others.

Bilateral symmetrical palsies of cranial nerves in 3 patients with inadequately controlled diabetes mellitus are described by Larson and Auchincloss.[28] One patient had fixed miotic pupils and bilateral weakness of the

seventh nerve, hypesthesia over the distribution of the fifth nerve bilat- ... in the ... The ... these disturbances was observed after satisfactory control of the diabetes

The case of Schick and Silbermann,[29] a diabetic with three separate attacks of paralysis of the third nerve, had a large area of calcification in the center of the sella turcica. Double vision due to hypoglycemia is always to be considered, but it is quickly relieved and therefore of temporary duration

[27] Root, Med Clin, North Amer, *16*, 985, 1933
[28] Larson and Auchincloss, Arch Int Med, *85*, 265, 1950
[29] Schick and Silbermann, Wien klin Wchnschr, *45*, 1255, 1932

Among 270 cases at the Mayo Clinic with palsies of the third, fourth, and sixth cranial nerves, Bailey[30] found only 10 diabetics He regarded cranial nerve palsies as being more frequently due to vascular lesions than to diabetes itself.

Ocular palsies with severe headache, occurred in four patients reported by Jackson.[31] Three were women, age 48 to 50 years and the fourth, a boy age four years, in whom other evidences of diabetic complications consisting of tendon reflex changes and retinal lesions were present In each case a congenital intracranial aneurysm was suspected, but not found

Goodman[32] *et al*, report one case of widespread neuropathy including severe attacks of pain in the distribution of the right trigeminal nerve

Pupillary Reactions.—Abnormal pupillary reactions have been reported [illegible]

spinal fluid examination Rundles also reports 2 cases with Argyll-Robertson pupils in whom no evidence of syphilis could be detected In others with sluggish light reflexes, he noted their return to normal with general neurologic improvement

Genito-urinary Disturbances—Atonic type of bladder paralysis occurred in 32 cases or 25 6 per cent of Rundles' series of 115 patients This type of so-called cord bladder has been reported several times as a manifestation of diabetic neuropathy McKittrick and Root[33] reported 3 cases, Jordan and Crabtree[34] 7 cases, Jordan[35] an additional 5 cases and Rudy and Muellner[36] 11 cases As emphasized by Jordan, this type of bladder disturbance is usually irreversible.

Successful treatment by transurethral resection of the bladder neck in three diabetic patients who had neurogenic vesical dysfunction associated with diabetic neuropathy is reported by Emmett, Daut and Sprague[37] The authors emphasize the particularly serious nature of the diabetic bladder because of the possibility of ascending infection Indeed, in one case subsequently the right kidney was removed because of multiple abscesses in the upper half of the kidney

Chemistry of Diabetic Nerves.- Chemical analyses of 52 nerves of diabetic patients and 23 nerves of non-diabetics at the Deaconess Hospital have been carried out in the laboratory of Prof W R Bloor, and the results reported by W R Jordan, I D Randall, and W R Bloor[38] In their two papers the literature is reviewed Their results show that the average phospholipid, cholesterol, and cerebroside content of diabetic nerves was

[30] Bailey Diabetes , 32 1954
[31] Jackson Brit Med Jour 2, 408, 1955
[32] Goodman *et al* The Diabetic Neuropathies Oxford, England, Blackwell, 1951
[33] McKittrick and Root Diabetic Surgery Philadelphia Lea & Febiger 1928
[34] Jordan and Crabtree Arch Int Med 55, 17, 1935
[35] Jordan loc cit p 486
[36] Rudy and Muellner Jour Urol , 45, 844 1941
[37] Emmett Daut and Sprague Ibid 61, 244, 1949
[38] Jordan Randall and Bloor Arch Int Med , 55 26, 1935

much lower than that of the nerves used for control. In Table 88 are shown the values for nerves from diabetic patients with arteriosclerosis as compared with normal averages.

TABLE 88.—LIPID CONTENT OF NORMAL AND DIABETIC NERVES. AVERAGE VALUE WITH RESPECT TO ARTERIOSCLEROSIS.

Arteriosclerosis	*No of Cases*	*Phospholipid, per cent*	*Cholesterol, per cent*	*Cerebroside, per cent*
1+ (slight)	1	3 85	1 15	1 60
2+	6	1 69	0 64	0 69
3+	12	1 67	0 60	0 77
4+ (advanced)	1	1 40	0 45	1 46
Normal average	—	*4 40*	*1.36*	*1 73*

A third report by Randall[39] also demonstrated that the peripheral nerves from such subjects showed marked decreases in phospholipids, cholesterol and cerebrosides and an increase in neutral fat. The posterior tibial nerve showed more extensive change than the sciatic and the latter more than the femoral. The greater extent of change in the more distal parts of the nerves suggested an inadequate blood supply and anoxemia. Vascular *disease was not the sole cause for these changes in chemical structure* of the diabetic nerves. Previous inadequate control of the diabetes seems to affect the nerve unfavorably, although a constant correlation between the severity and duration of the diabetes and the extent of the chemical changes was not shown.

The use of the words "peripheral neuritis" is hardly applicable to many forms of diabetic neuropathy. Lesions such as sphincter abnormalities, and sexual impotence result from inadequacy in the spinal roots and spinal cord and of the autonomic system. The word "neuronitis" may be more appropriate as indicating the fact that in true diabetic neuropathy the entire neuron may be involved. Handlesman[40] in discussion of Rundles' work gave an anatomical interpretation asserting that the diabetic neuritis is [illegible]

[illegible]

this common condition is fragmentary. Typically, diabetic neuritis is [illegible] postmortem [illegible] ...e [illegible] ...al

change. Fraser and Bruce[42] have described demyelinisation of the posterior tibial nerve in a man with diabetes and neuritis.

Of the various types of neuropathy, the one which has been most extensively studied and reported in the literature is ischemic neuropathy. Woltman and Wilder[43] reported the results of eight amputation specimens from cases with neuritic symptoms in addition to two cases in whom the

[39] Randall. Jour. Biol. Chem., *125*, 723, 1938.

spinal cord was examined at autopsy. In their view changes in the spinal cord were minimal. Even when there was previous clinical evidence of diabetic pseudotabes, any degeneration in the cord that was observed seemed to be explicable by senility and arteriosclerosis. The peripheral nerves … Degeneration of … the nerves examine… associated with th… most significant factor in the production of these lesions. Vascular disease and arterial blood supply are also stressed by Kauvar,[44] Roberts,[45] Richards,[46] Barker,[47] Goldsmith[48] and deTakats.[49]

Whether all types of diabetic neuropathy arise from a primarily vascular process is most uncertain. Certainly the known reversibility of the neuritic process in most cases suggests that reversible, metabolic factors are also important. Those investigators who have been impressed with the therapeutic success of vitamin B_1, liver extract and vitamin B_{12} all favor the viewpoint that diabetic neuritis is essentially a deficiency disease.

Etiology.—Although diabetic neuritis has been attributed to many …

of unregulated diabetes, a conclusion supported recently by Goodman.[50]

Insulin deficiency leads to impairment of carbohydrate utilization, both …

of nerve tissue. At the same time, protein and fat undergo preliminary oxidation in the liver with the production of ketone bodies, which are normally oxidized in the periphery. … nervous syster… ketone bodies… utilization, ke… athy appears … nutrition. Under normal conditions, carbohydrate is the principle type of food utilized in the metabolism of nervous tissue.[51] Some energy is derived from the breakdown of phospholipins and phosphocreatin. Although the brain can metabolize glucose … that any disease interfering … neuropathy. Thus thiamine …

[44] Kauvar: Jour. Clin. Endocrinol., *1*, 955, 1941.
[45] Roberts: Am. Heart Jour., *35*, 369, 1948.
[46] Richards: Jour. Neur. Neurosurg. and Psych., *14*, 76, 1951.
[47] Barker: Arch. Int. Med., *42*, 271, 1938.
[48] Goldsmith and Brown: Am. Jour. Med. Sci., *189*, 819, 1935.
[49] deTakats: Loc. cit., p. 493.
[50] Goodman: Am. Jour. Digest. Dis., *22*, 236, 1955.
Stadie: Bull. New York Acad. Med., *19*, 778, 1941.
[51] Best and Taylor: Pp. 916–918, loc. cit., p. 165.
[52] Himwich: Brain Metabolism and Cerebral Disorders, Baltimore, Williams and Wilkins, p. 21, 1951.

in carbohydrate metabolism wherein there is a failure of pyruvic acid oxidation.[54] No comparable abnormality is known in diabetes. If abnormal carbohydrate metabolism, leading to neuron starvation, proves to be a common denominator in different types of neuropathy it may be unimportant in terms of end results, if the defect occurs at the 6 carbon stage, as in diabetes, or at the 3 carbon stage. (Rundles).

Arteriosclerosis has long been incriminated as a probable etiological factor and, as shown by Woltman and Wilder, may well be associated with the neurological factors in the ischemic type of neuropathy. Any association, however, between arteriosclerosis and the typical acute reversible neuritis often found in young diabetics seems remote.

Although vitamin deficiencies may occur in diabetic patients just as in non-diabetic patients, and the mild neuritic symptoms in the 8 patients apparently cured with thiamine chloride by Fein, Ralli and Joliffe[55] may well represent a vitamin deficiency, we strongly concur with the opinion expressed by Rundles that he has "never seen clinical improvement in diabetic neuropathy by any treatment regimen in the absence of effective diabetic control." Analyses of the vitamin content of diabetic diets by Jordan,[56] Needles,[57] and Rundles[58] did not indicate significant deficiencies

We have been unable to attribute an etiological role in the 2000 cases of diabetic neuropathy studied at the Deaconess Hospital to anemia, alcohol, dietary deficiency, drugs, infection, or lead poisoning.

Treatment.—Unless the diabetes is brought under control by insulin and diet, all other therapy is of no avail, hence the salient point in treatment should be to acquire and maintain meticulous diabetic control Initial hospitalization is usually necessary in order to obtain the best results Insulin should always be given.

Standard diabetic diets with carbohydrate 150 to 200 grams, protein from 90 to 120 grams and adequate caloric content are satisfactory. The typical loss of appetite may require special foods until with improvement in the neuropathy appetite becomes normal. Although most diabetics who develop neuropathy have basically only mild or moderate diabetes, a great increase in severity and in insulin need may accompany the decompensation of neuropathy The need for larger doses of insulin may persist for months

The use of vitamins is unsettled but certainly does no harm unless one substitutes their use for attempts to control the diabetes The whole B complex supplemented with thiamin chloride is most frequently used, but striking improvement with their use must not be expected or promised In some patients with neuritis, the pain may at times interfere with the adequate intake of food and in these cases especially the use of vitamins may prove rational

Ordinarily the relief of pain is the main concern of the patient and this requires immediate attention Salicylates in the form of aspirin or sodium salicylate gr 5 to 10, repeated frequently, may prove adequate, but salicy-

[54] Peters Lancet, *1*, 1161, 1936

[illegible] J. Am. M. Ass., *115*, 1973, 1940

[illegible] '22, 1939

[illegible] Yor

lism must be borne in mind. Local warmth with blankets may help, but

cradle over the foot of the bed to suspend the covers over the lower extremities is helpful when hyperesthesia is marked. Opiates must be used cautiously but when needed codeine should not be withheld.

When the painful neuritis is well localized or restricted to the territory of a single peripheral nerve, Rundles considers the advisability of local anesthesia, nerve crush or nerve section, but feels that results obtained have not been encouraging and we must warn against such strenuous measures.

If foot drop is present, support for the plantar surface of the foot is supplied and a wire hoop placed over the foot of the bed to counteract the pull of the covers, in an effort to prevent contractures of the calf muscles.

Sancetta *et al.*,[59] used vitamin B_{12} in the management of the neurological manifestations of diabetes and obtained considerable relief from pain. Dosage recommended was 15 to 30 micrograms daily for one to two weeks, later maintaining the patient on the same dose given once or twice weekly. In a few cases massive doses of B_{12} were used, but without any better effect than obtained with the usual schedule. They advise such large doses only when the patient appears to be refractory to the treatment.

Lobotomy has been performed in a few diabetic patients for relief of severe pain.

Mild cases usually respond to therapy in a few weeks, moderate cases take several months to a year and severe ones may require one to several years for complete recovery. For the severer cases, encouragement is needed and it is well worth while to show the patient a cured case as proof of recovery. Patience both on the part of the doctor as well as the patient is necessary.

B. UNUSUAL MANIFESTATIONS OF DIABETIC NEUROPATHY

Charcot Joints.—The concurrence of neurotrophic bone changes in the foot as a complication of diabetes has been pointed out by Root,[60] Jordan,[61] Foster and Bassett,[62] Rundles,[63] Muri,[64] Wilson and McIntyre,[65] and Beidleman and Duncan.[66] It is noteworthy that in these case reports the association of diabetic neuropathy, Charcot joint, retinitis and the diabetic nephropathy frequently appears. Bailey and Root[67] studied 20 diabetic patients with foot lesions simulating the Charcot joint yet with no evidence of central nervous system syphilis. The earliest gross change detected in the foot is a thickening of the tarsal region which tends to progress slowly and eventually to become a thickened deformed foot with

[59] Sancetta, Ayres and Scott. Ann. Int. Med., 35, 1028, 1951.
[60] Root. New York State Jour. Med., 42, 2206, 1942.
[61] Jordan. Loc. cit., p. 486.
[62] Foster and Bassett. Arch. Neurol. and Psychiat., 55, 173, 1946.
[63] Rundles. Loc. cit., p. 498.
[64] Muri. Acta Med. Scand., 135, 391, 1949.
[65] Wilson and McIntyre. Calif. Med., 70, 420, 1949.
[66] Beidleman and Duncan. Am. Jour. Med., 12, 43, 1952.
[67] Bailey and Root. New England Jour. Med., 236, 397, 1947.

in carbohydrate metabolism wherein there is a failure of pyruvic acid oxidation[54] No comparable abnormality is known in diabetes. If abnormal carbohydrate metabolism, leading to neuron starvation, proves to be a common denominator in different types of neuropathy it may be unimportant in terms of end results, if the defect occurs at the 6 carbon stage, as in diabetes, or at the 3 carbon stage. (Rundles).

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[54] Peters Lancet, *1*, 1161, 1936
[55] Fein, Ralli and Joliffe Jour Am Med Assn, *115*, 1973, 1940
[56] Jordan Loc cit, p 486
[57] Needles Arch Neurol and Psychiat, *41*, 1222, 1939
[58] Rundles Medicine, *24*, 111, 1945, Bull New York Acad Med, *26*, 598, 1950

he appeared cachectic, and marked generalized muscular atrophy was present. Impairment of the absorptive function was shown by a characteristic puddling of barium in terminal ileum. Failure of absorption was specific in that the protein absorption seemed to be normal, but lipid absorption was deficient and muscle fibers were found in the stools. No achlorhydria was present and the bone marrow picture was not due to pernicious anemia. Osteoporosis was present with unclosed epiphyses. The voice was high-pitched and prepuperal genitalia were noted. We are indebted to the Peter Bent Brigham Hospital for further studies. All parameters of pituitary function appeared normal except FSH, which was very low. A testicular biopsy revealed hypoplastic tissue with no spermatocytes [illegible]

Forty cases of this diarrhea occurring in diabetic patients in the Joslin Clinic were reported by Sheridan and Bailey,[71] and 56 additional cases were observed between 1946 and 1951. In this series of 96 cases diarrhea occurred chiefly at night. Alternating diarrhea and severe constipation were frequently noted, as was true in Rundles' series.[72] It tended to occur intermittently in 80 per cent with remission lasting for several days followed by relapse. Nocturnal incontinence of feces occurred in 75 per cent of the cases.

C. DISORDERS OF THE NERVOUS SYSTEM AS COMPLICATIONS OF DIABETES

Introduction.—The relation of carbohydrate, protein and fat metabolism to emotional states, mental illness and convulsive disorders has been a matter for intensive studies and many publications. From time to time, important trials in court have turned upon problems of the effect of hypoglycemia, insulin action, or acidosis. The correlation of data regarding the biochemical behaviour of brain and nerve *in vitro* with facts in the living organism, has just begun.[73] In man, the brain in the resting state consumes from one fifth (adults) to one half (children) of the body's oxygen supply.[74,75] This intense activ [illegible] electrical activity [illegible] olism of the nervo[illegible] whole brain in man and animals is unity. The brain and probably the peripheral nerves derive almost all their energy from glucose and oxygen. Energy derived from amino acid pathways and from fat, if significant, is small. However, this dependence for energy upon carbohydrate does not exclude a necessary metabolic turnover of protein, lipids and amino acid.[75a]

[70] Berge, Wollaeger, Scholz, Rooke and Sprague: Diabetes, 5, 25, 1956.
[71] Sheridan and Bailey: Jour. Am. Med. Assn., 130, 632, 1946.
[72] Rundles: Loc. cit., p. 498.
[73] Hicks and Warren: Introduction to Neuropathology, New York, McGraw-Hill, p. 221, 1950.
[74] Kennedy: In Korey and Nurnberger: Neurochemistry, New York, Harper, p. 230, 1956.
[75] Elliott, Page and Quastel: Neurochemistry, Springfield, Ill., C. C Thomas, p. 61, 1955.
[75a] Geiger: Physiol. Rev., 38, 1, 1958.

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and no development of the Leydig cells The clinical picture was consistent with eunuchoidism of the usual variety reflecting lack of specific pituitary hormones His sudden death at home was unexplained.

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[70] Berge, Wollaeger, Scholz, Rooke and Sprague Diabetes, *5*, 25, 1956

[71] Sheridan and Bailey Jour. Am. Med. Assn., *130*, 362, 1946

[72] Rundles Loc. cit. p. 498

[73] Hicks and Warren Introduction to Neuropathology, New York, McGraw, Hill, p. 221, 1950

[74] Kennedy In Korey and Nurnberger Neurochemistry, New York, Harper, p. 233, 1956

[75] Elliott, Page and Quastel Neurochemistry, Springfield, Ill., C. C Thomas, p. 61, 1955

[76] Geiger Physiol. Rev., *38*, 1, 1958

A study of diabetic patients should provide a means for correlating biochemical data and disturbances in the central nervous system.

Emotion.—That the level of the blood sugar may be affected by emotion has been frequently reported. The fact that some emotions cause hyperglycemia, whereas on other occasions response to emotion is that of hypoglycemia, is explained by Altschule,[76] who quotes the work of Schou.[77] Schou has shown that the blood sugar rises to a maximum three quarters of an hour after the emotional experience, then comes back to normal or well below normal. Thus, according to the time of measurement, high, normal, or low values may be encountered. Studies of the blood sugar in cases of neurosis show, usually, normal fasting values and glucose tolerance curves; but low fasting values and flat glucose tolerance curves are sometimes observed. At times the relationship is obscure, since the symptoms of hypoglycemia and those of psychoneurosis are similar.[78]

rine and the adrenocorticoids, themselves under the control of the hypothalamic-pituitary complex.

Psychoses.—Metabolic studies in manic-depressive, involutional, and schizophrenic psychoses indicate that blood sugar levels are usually unaffected. The incidence of glycosuria in psychotic patients varies with different reports. It is stated that treatment with electric shock or insulin therapy may initially cause worsening of glucose tolerance, but at the end of a course of such treatment, glucose tolerance is often improved. A

the urine or blood of patients in preventing the action of insulin when injected in animals has been studied.

a. Manic-depressive psychosis has been treated by electric shock therapy in twenty of our diabetic patients, but in no case has insulin shock treatment been applied. Dr. O. J. Raeder, Dr. Robert Fleming and Dr. H. H. Tucker have directed treatment with uniformly good results. Prior to electric shock treatment, three such patients were greatly helped by lobotomy.

b. Schizophrenia has been recognized in only ten patients in recent years.

c. Senile Dementia.—Senility, often premature, is a common and an extremely important problem. Not infrequently elderly diabetic patients with cerebral arteriosclerosis show mental confusion for the first time in the hospital, especially following surgical procedures and particularly at

[76] Altschule: Bodily Physiology in Mental and Emotional Disorders, New York, Grune and Stratton, 1953.
[77] Schou: Acta Psychiat. Neurol. Scand., Suppl., 14, 1937.
[78] Editorial: British Med. Jour., *1*, 150, 1958.

night Among the early symptoms of senility are changes in business judgment and the power of decision which, when combined with irritability, may lead to consequences most distressing to business associates, family and friends. The diagnosis, therefore, of the onset of changes which are destined to be progressive is one of great practical importance Dr O J Raeder in consultation has helped with a number of such problems

Epilepsy and Related Disorders.—The incidence of epilepsy among

diabetic, who suffers from convulsions or seizures, in which confusion, delirium ... the possibility that hypo-

m or as

s of the

ency or

lesions of the central nervous system. A whole range of symptoms may occur with or without serious brain damage (See page 314) The effects of hypoglycemia are not constantly related to the actual blood sugar level but sometimes to the speed with which the blood sugar declines. However, the effects of hypoglycemia vary in different portions of the brain and in different individuals under genic and other influences[79, 80, 80a] In metabolic terms, brain tissue is protected during hypoglycemia by a change to fat oxidation[81] Himwich quotes Root and Carpenter,[82] whose diabetic patient was given 100 units of insulin fasting plus 50 grams of glucose The

that diabetic patients are more sensitive to hypoglycemia than are normal individuals The relation, therefore, of hypoglycemia to permanent damage and the possible induction of epilepsy is a serious problem It should be remembered, however, that hypoglycemia in mild degree occurs daily in thousands of diabetic patients without any serious immediate symptoms or any evidence of later damage

The discovery of insulin raised the hope that hypoglycemia, constant or paroxysmal, might be shown to be a factor of importance among epileptic patients Lennox[83] studied blood sugar levels of many diabetic patients and the glucose tolerance curves of 140 It appears that glucose played only a passive role with respect to epileptic convulsion Among some

[79] Hicks Arch Path 49, 111 1950
[80] Hicks and Cox Ibid 65 378 1958
[80a] Condon, Becka and Gibbs New England Jour Med, 251, 638, 1954
[81] Himwich Brain Metabolism and Cerebral Disorders Baltimore, Williams and Wilkins, p 24, 1951
[82] Root and Carpenter Am Jour Med Sci, 206, 234, 1943
[83] Lennox Epilepsy and Related Disorders Boston, Little, Brown Co, in press

100,000 total admissions to Harriet Lane Home in Baltimore, there were only 15 with convulsion ascribed to hypoglycemia Three were diabetic and two had adenomata of the islets of the pancreas.

Induced Hypoglycemia.—Manfred Joshua Sakel (1900) in 1934 demonstrated that involuntary movements and unconsciousness when induced by insulin could improve the mental state of persons with schizophrenia In 1937 the Gibbses and Lennox charted the contrary effects of insulin [illegible] stopping a veritable hurricane [illegible] y noted that such a hurricane [illegible] ys of calm They gave insulin and then glucose to 34 epileptics. The hypoglycemia did not cause an *increase of fast activity in patients subject to grand mal, nor did it alter* petit mal variant formations, but the three-per-second spike-wave discharges of petit mal were greatly increased if the blood sugar fell below 50 mg per 100 cc., a level which did not cause altered hypoglycemic symptoms

In the diabetic epileptic, in general, *a reciprocal relationship exists*, the higher the blood sugar the fewer the seizures and vice versa. However, such correlations are not dependable In one 18-year-old boy described by Lennox, convulsions had been preceded by symptoms of hypoglycemia. [illegible] Given 120 units [illegible] and stupor, but the EEG contained only the large, slow components characteristic of hypoglycemia In this case the drastic reduction in the amount of circulating sugar failed to do what the patient's epileptic nature had done without any demonstrable assistance

According to Lennox,[84] *cerebral dysrhythmia is found in 8 to 10 per cent* of non-diabetic persons This parallels the incidence of 8 per cent noted in routine electro-encephalography in our uncomplicated adult diabetics. This material was presented by Greenblatt, Murray and Root [85] Fifty-one per cent of patients who complained of frequent severe insulin reactions, however, *had abnormal electroencephalograms* This would seem to indicate that some diabetics who seem unduly difficult to regulate may have cortical instability, and that relatively minor drops in blood sugar may give marked clinical reactions The character of these "reactions" varies widely, from dizziness, speech disturbances, paresis and temper tantrums to attacks of petit mal, spells of unconsciousness and generalized convulsions The electroencephalograph has proved invaluable in differentiating these attacks from true epilepsy, and we have been fortunate in the past few years to have available the facilities and cooperation of the electroencephalographic departments of the Neurological Institute of the Children's Medical Center and of the Boston Psychopathic Hospital

Many of our patients with true epilepsy have received *Sodium Dilantin*, Phenobarbital, or newer drugs Severe maniacal psychomotor seizures

[84] Lennox *Loc cit*, p 503
[85] Greenblatt, Murray and Root *New England Jour Med*, *234*, 119, 1946

requiring such surgery as resection of a temporal lobe have not been seen in our patients at the New England Deaconess Hospital.

ency results in violence In such patients, the periods of amnesia commonly

Blurring of vision may occur in this period In 116 cases Balodimos and Root[83a] noted the long duration of diabetes with insulin treatment for an average of 18 years. Rarely did such reactions occur after periods as short as 2 to 5 years The insulin dosage in 97 cases was between 20 and 60 units daily A neuropathy affecting the central nervous system or the sympathetic system with impaired recognition of the usual symptoms might explain these serious reactions

Accidents.—States of diminished consciousness may occur in diabetic patients from such causes as hypoglycemia, reduction in oxygen, cerebral circulation or intracellular metabolic defects, and play an important role in accidents In a study of over 1200 diabetic adults at the New England Deaconess Hospital,[84] made possible by the cooperation of Professor Ross A McFarland, a total of 266 automobile accidents was reported by 196 patients (among 586 drivers) Other accidents, numbering 606 in 364

careful teaching in the management of his diabetes, had experienced fewer automobile accidents than his non-diabetic spouse The effect of ketosis or of hypoglycemia seemed to be magnified in the presence of other toxic agents such as hypoxia, alcohol or sedatives

Air transportation may present new problems in the jet age Accidents occurring during flights at levels of 35,000 to 40,000 feet and at excessive speeds will require changes in airplane design and construction, with particular stre

where bare

grave Esp

possibility

accidents have already occurred in scheduled operations in which the pilot in command was subsequently found to have diabetes Medical certification by the Civil Aeronautics Administration is denied to airmen who are true diabetics [84]

[83a]Balodimos and Root To be published

[84]McFarland Human Factors in Air Transportation New York, McGraw-Hill Book Company P 240 287 749 1953

Air travel for patients is not contraindicated if they are under good diabetic control and follow prescribed time schedules for insulin and meals conscientiously.

Miscellaneous.—Cerebro-vascular accidents, referred to on page 483 in marked contrast to coronary occlusion or gangrene, do not occur with any greater frequency in diabetic than in non-diabetic patients. Subarachnoid hemorrhage may simulate diabetes, as was true in Case 8517, age 11 years, who became unconscious at 3:00 A.M. on December 1, 1929. In a nearby hospital, the urine contained much sugar and the spinal fluid sugar was 408 mg. per 100 cc. She received 157 units in the first 13 hours. The spinal fluid was bloody. Recovery was followed by a second such hemorrhage one year later. Since that time she has been entirely well, without diabetes. Subdural hematomata occurred in a husband and wife, both diabetic, as a result of an automobile accident. When symptoms developed two weeks later, the husband was operated upon successfully; but the wife died on the way to the operating room. Cerebellar hemorrhage in an 8-year-old child simulated diabetic coma. *After operative drainage of the area of hemorrhage, complete recovery from nystagmus and ataxia occurred* without residual diabetes. Among 100 cases studied at autopsy, infarction of the brain, without thrombosis, was found in 60 cases.[86] Of these ten were diabetic.

Myasthenia gravis, recognized in five of our patients with diabetes, may be considered in the diagnosis of bulbar palsies, such as ptosis, or other ocular palsies. The use of the prostigmin test or of Tensilon as a diagnostic procedure may be decisive if immediate improvement of ptosis or muscular weakness occurs.

The frequency of such conditions as paralysis agitans, meningitis and encephalitis, herpes zoster, multiple sclerosis, Friedreich's ataxia, brain tumors and suicide seems no greater than would be expected in a large hospital series of diabetic patients. The neurologic manifestations of periarteritis nodosa are notable in relation to the differential diagnosis in diabetic neuropathy.[87]

[86] Hicks and Warren. Arch. Path., *50*, 403, 1951.
[87] Raeder and Root. Rev. Neurol., *92*, 511, 1955.

Chapter 19

THE GENITO-URINARY SYSTEM

Revised by HOWARD F ROOT, M D

A GENERAL CONSIDERATIONS

WITH the increased longevity of diabetic patients, the genito-urinary system has assumed a new importance The true diabetic nephropathy has become the major factor among the causes of morbidity and mortality in diabetes which has its onset early in life In the development of this nephropathy, infections of the urinary tract and especially of the kidneys are important factors. The characteristic Kimmelstiel-Wilson lesion of intercapillary glomerulosclerosis is accompanied by arteriolosclerosis and arteriosclerotic changes, which justify considering this condition in relation to cardio-vascular disease and to the retinal complications which are so clearly related to it (See Chapter 15) Infections of the urinary tract, neuropathic disturbances, prostatic hypertrophy or neoplasms make up the bulk of other lesions commonly encountered

B INFECTIONS OF THE URINARY TRACT

The gravity of urinary tract infection is indicated by clinical experience and particularly by post-mortem examinations In 422 autopsies performed at the New England Deaconess Hospital from 1919 to December 1, 1945, infection of the genito-urinary tract was found in 85 cases or 20 per cent [1,2] From December 1, 1945, to September 1, 1950, 30 per cent, and from 1950 to 1957, (January 1) in 414 autopsies, 169, or 40 8 per cent showed significant urinary tract infections Previous studies have indicated both the incidence and the importance of urinary tract infection [3,4]

The use of chemotherapeutic and antibiotic agents has revolutionized the treatment of urinary tract infection Practically all the organisms that invade the urinary tract are to some degree sensitive to one or a combination of the agents now available Such conditions as pyelonephritis of pregnancy, Proteus vulgaris, Pseudomonas aeruginosa, and Streptococcus fecalis urinary tract infections, which were formerly managed with little improve-

[1] Bernard Story and Root New England Jour Med 248 136, 1953
[2] Joslin *et al* P 491 Loc cit p 416
[3] Sharkey and Root Jour Am Med Assn 105, 2231 1935
[4] Weiss and Parker Medicine 18 221 1939
[5] Baldwin and Root New England Jour Med, 223 244 1940
[6] Harrison and Bailey Jour Am Med Assn 118, 15, 1942
Bowen and Kutzman Ann Int Med 17, 427 1942
[7] Rhoads, Billings and O'Connor Jour Am Med Assn, 148, 165, 1952

TABLE 89.—186 CASES OF MEDULLARY NECROSIS OF THE KIDNEY

Year of Publication	Author	Diabetes Present			Diabetes Absent
			Urinary Obstruction		
			Absent	Present	
1877	Friedreich[9]			1	
1888	Turner[10]		1(1)		2(1)
1899	Stoudensky[11]			6(5)	
1926	Artusi[12]				1
1931	Schömer[13]		1		2
1934	Grauhan[14]			2(2)	
1934	Foulon[15]				1(1)
1937	Froboese[16]		9(7)		1
1937	Günther[17]	2(2)	6(1)	2	
1937	Praetorius[18]			1(1)	
1937	Sheehan[19]			1	
1938	Junker[20]		1(1)		
1938	Alken[21]		4(4)		
1939	Schneider[22]				1(1)
1941	Mellgren[23]			1	1
1939	Olsson[24]		1(1)		
1942	Overzier[25]			1(1)	
1942	Harrison[26]		3(1)		
1944	Davson[27]				1
1945	Eskelund[28]				1
1946	Robbins[29]		19(2)	6	1
1947	Edmondson[30]	8(4)	21(4)	20(9)	1(1)
1947	Pellegrin[31]		1		
1947	Dahlmann[32]		1(1)		1
1948	Richfield[33]		1		
1948	Stevens[34]		1		
1948	Moore[35]		1		
1949	Welch[36]		1		
1949	Robbins[37]	2(1)	6(3)	5	1
1950	Gaustad[38]	3(2)	2(2)	1(1)	
1950	Muirhead[39]		1	1(1)	1
1953	Silberstein[40]		1		2
1954	Wall[41]		2		1
1954	Garrett[42]		5	1	
1955	Sargent[43]		1(1)		
1956	Whitehouse[44]		11(8)		
1958	Hashim[45]	1	1		
		16(9)	102(37)	49(20)	19(4)
	TOTAL	118(46)		68(21)	

[9] von Friedreich Virchow's Arch f path Anat, *69*, 308, 1877
[10] Turner Trans Path Soc London, *36*, 268, 1885, Ibid, *37*, 290, 1886, Ibid, *39*, 159, 1888
[11] Stoudensky Ztschr f Heilk, *20*, 459, 1899
[12] Artusi Beitr z path Anat u z allg Path, *75*, 1, 1926
[13] Schomer Frankfurt Ztschr f Path, *41*, 265, 1931
[14] Grauhan Ztschr f Urol, *28*, 462, 1934
…h, *11*, 416, 1934
… Gesellsch, *30*, 431, 1937
84, 1695, 1937
937

[21] Alken Ibid 32, 465, 1938

ment, are now managed successfully. Treatment at the present time is so simplified that the tendency is to treat the patient's signs and symptoms

however that few infections indeed are primary in origin. With rare exceptions investigation will uncover the reason for the onset of infection

Proper management depends upon (1) identification of the organism, ... the urinary tract, and

... the kidney confined to the distal parts of the pyramids and not resulting from purulent destruction, pressure, atrophy, obstruction of a large blood vessel or intoxication have been known for some time Thus ischemic necrosis of the renal

December 1955, eleven such cases have been recognized in the New England Deaconess Hospital and reported by Whitehouse and Root [47]

The incidence of pyelonephritis found at the autopsy table is from 18 to 22 per cent of diabetic patients but in only 3 5 to 4 0 per cent of general post-mortem material Of 859 diabetic patients autopsied at the Los

with severe pyelitis 27 per cent

Schneider Ibid 32, 777, 1938

Mellgren, and Redell Acta Chir Scand, 84, 439, 1941

Olsson Acta Radiol, 20, 578, 1939

Overzier Virchow's Arch f path Anat, 309, 600, 1942

Harrison, and Bailey Jour Am Med Assn 118, 15, 1942

Dawson and Langley Jour Path and Bact 56, 327, 1944

Eskelund Acta radiol, 26 548, 1945 Abstracted, Jour Am Med Assn, 130, 1192, 1946

Robbins, Mallory and Kinney New Englnd Jour Med 235, 885, 1946

Int Med, 79 148, 1947

ll, 5, 66, 1947

17

est Virginia Med Jour 44, 12, 1948

1949

77 773 1949

nd, 136 341 1950

Am Med Assn, 142, 627 1950

38 689 1953

Wall Jour Urol 72 1 1954

Garrett, Norris and Vellios Ibid 2 609 1954

Sargent and Sargent Ibid 3 757 1955

Whitehouse and Root Jour Am Med Assn 162 444 1956

Hashim Diabetes 114 1958

Mandel Amer Jour Med 13 322 1952

Whitehouse and Root Loc cit p 509

Edmondson Martin and Evans Loc cit p 509

To the 160 cases of papillary necrosis gleaned from the literature by Mandel[49] we have added 26, including 12 cases at the New England Deaconess Hospital It will be seen that diabetic cases greatly outnumber non-diabetic and that *urinary tract obstruction is rare in the diabetic.* Unilateral cases (shown in brackets) total 70.

In the New England Deaconess Hospital series, one unilateral case was operated on successfully and lived for two years. Eleven were found in the course of 266 post-mortem examinations, or 1 in every 24 cases autopsied, an incidence of 4 1 per cent. The average age of our patients at the time of diagnosis was 60 years, the youngest 26 years, and the oldest 79 years.

Clinical Diagnosis and Treatment—Success in treatment depends upon early detection However, symptoms of the primary or associated disease usually mask the presence of the renal lesion In our cases two clinical pictures were associated with the condition (1) The acute, fulminating type which is characterized by severe prostration and signs of overwhelming sepsis. Among the frequent findings reported are flank pain, dysuria, urinary urgency and frequency, proteinuria, pyuria, bacteriuria, microscopic to massive hematuria, oliguria and anuria; azotemia, chills, fever, *nausea, and vomiting, stupor and coma (with or without diabetic acidosis)* (2) A subacute type was characterized by smouldering renal infection, present for weeks or months, with acute exacerbations and terminal oliguria and uremia An asymptomatic form was also recognized in our group. Laboratory findings included leucocytosis, non-protein nitrogen level between 40 mg. and 100 mg , in one case 175 mg. per 100 cc., albuminuria, hematuria, pyuria Cylindruria was recorded in occasional cases

The following case was reported by Hashim[50] A woman, age 59 years, (Case 4812) entered the New England Deaconess Hospital October 13, *1936, for adjustment of diabetic tr*
polyuria, polyphagia, weakness, an
three months prior to admission.
or
U
ce
blood cell cast Subsequently the sediment showed many more white cells Non-protein nitrogen, two days after admission, was 25 mgs per cent White blood count was 16,000 on admission, and three days later rose to 25,500 On the third day, chills and a fever of 104 degrees with nausea and vomiting came on suddenly Retrograde pyelogram suggested necrotizing papillitis On the fifth day a tender mass could be felt on the right flank On the tenth day a diagnosis of necrotizing papillitis was *established by pathological examination of the small piece voided in the* urine On the eleventh day a right nephrectomy was carried out. The patient did well for five days when she suddenly relapsed into coma and her blood pressure was not obtainable The diagnosis of adrenal insufficiency was made During the next three days she was maintained on intravenous hydrocortisone and levophed At first she showed a slight improve-

[49] Mandel, Loc cit , p 509
[50] Hashim Loc cit , p 509

ment with recovery of consciousness Three days later, however, suddenly she stopped breathing. Post-mortem examination showed both her adrenal glands converted to a globular shaped mass by massive hemorrhage. The development of Waterhouse-Friderichsen syndrome was accepted as the cause of death Only one other such association of this syndrome with necrotizing papillitis is known

Necrotic tissues, sequestered in rare instances, have been excreted or obtained through cystoscopy Unilateral lesions in our New England Deaconess Hospital cases were frequent and perhaps explain the comparative lack of symptoms

Roentgenologic findings include demarcation and separation of the papillae with ring shadows due to disappearance of the papillary tip and

advanced pyelonephritis, often with abscess formation Bacteria were found in quantity

Pyelonephritis.—*Laboratory Diagnosis.*—The clinical features of acute pyelonephritis including tenderness to palpation and pain in the renal area, chills, fever, dysuria, pyuria, nausea and vomiting are well known

Omitting here any con-
boratory procedures are mentioned

(a) *Microscopic Examination of the Urine* - Pyuria may be defined arbitrarily as the presence of five or more white blood cells per high-power field in a centrifuged specimen of urine obtained by catheterization of the bladder or even from the kidney pelves Its absence must not be construed as evidence of absence of bacilluria or cause of active infection. (1) The "glitter cells," polymorphonuclear leukocytes whose granules show brownian movement are frequently found in the urinary sediment of patients with pyelonephritis and their persence has been used as a means of differentiating this condition from cystitis The special Sternheimer-Malbin stain may be used and this makes possible both recognition and study of other formed elements Our experience at the New England Deaconess Hospital with this stain did not indicate that final reliance should be placed on the presence or absence of these cells although their repeated occurrence

Berman, Schreiner and Feys New England Jour Med, 255 989, 1956
Kass and Schneiderman Ibid, 256 556 1957
Gutre and Beeson Ibid 255 474 1956
Beeson Yale Jour Biol and Med 28 81, 1955
Kass Am Jour Med 18 764 1955
Mansfield Mallory and Ellis New England Jour Med, 229 387 1943
Rhoads Billings and O'Connor Jour Am Med Assn, 148 165 1952
Jackson Dallenbach and Kipnis Med Clin North America, 39, 297, 1955
Sanford, Favour, Mao and Harrison Am Jour Med, 20, 88, 1956

stained smears of uncentrifuged urines have been used to distinguish infection from contamination, but this depends upon the presence of bacilluria in high count.

(*b*) *Bacteriologic Data.*—The fact that the urethra, both male and female, frequently contains bacteria makes it possible that any catherization will introduce bacteria into the bladder. The urine is an exellent culture medium, and therefore, reports of examination by culture in patients who may have had catherization, must be interpreted with care. Ascending infections have been frequent with the indwelling catheter. (1) Cultures of the urine may be obtained by catheter, or even after voiding, provided special local cleansing preparation has been carried out Sensitization tests against the various antibiotics will frequently give the clue to the selection of the appropriate drug (2) Bacterial counts up to 10,000 bacteria per ml of urine frequently represent contamination Counts exceeding 100,000 are usually found only in patients with active renal infection Counts between these figures may be found in patients with active infection Lower counts will occur if a bacteriostatic agent is present or if the rate of urine flow is rapid so that no pooling of urine for a period of time occurs, if bacteria do not grow well, if there is obstruction of the ureter and finally if infection is limited to certain areas in the kidney.

At the New England Deaconess Hospital, from December 1, 1945 to January 1, 1956, 186 patients were treated for diabetes complicated by pyelonephritis There were 157 females and 29 males with an average age of 53 years and an average diabetic duration of 12 years. The youngest patient was a male aged 18, the oldest a female age 90. The insulin dosage varied from none to 90 units Duration of diabetes varied from three months to thirty-nine years, but for the most part the diabetes was of long duration as seen by the average It must be emphasized that diabetic control was considered generally poor.

Mixed infections were frequent, but the most common organism was the Escherichia coli Six males and 18 females were found to have pure cultures. Organisms found in 75 patients were as follows. Escherichia coli 33, Streptococcus non-hemolyticus 17, Aerobacter aerogenes 15, Staphylococcus

England Deaconess Hospital, 51 out of the first 52 diabetic patients referred to it were women, nine having acute and chronic cystitis and the remaining

species on subsequent culture after the original bacteria had disappeared

[60] Bernard, Story and Root Loc cit, p 507

under treatment; pseudomonas or proteus infection often displaced the original infection. Positive cultures without urinary symptoms have been reported frequently, especially in diabetic women, so that asymptomatic urinary tract infections may flare up under the influence of new infections, particularly the colon group or under other adverse conditions. It is extremely difficult to render the urine of these patients sterile upon culture.

bicarbonate.

The following antibiotics were used during hospital stay: procaine penicillin, streptomycin, aureomycin, chloramphenicol, terramycin Bacitracin was also tried

grade, is essenti

staphylococcus ,

furuncles, carbuncles, foot infections, gangrene, cellulitis or septicemia Although the hematogenous cases form 55 per cent of the ascending urinary tract infections, they are usually due to the E coli, a fact particularly im-

In recent years the assumption has been expressed that nothing can be accomplished in the treatment of chronic pyelonephritis Certainly little

This policy of immediate treatment of urinary tract infection and aggressive eradication of causal factors is particularly necessary in pyelonephritis It must be remembered that the diabetic of long standing may not have the early symptoms of frequency and dysuria It is contingent upon the physician, therefore, to make the diagnosis by examination of urinary sediment and to secure follow-up examination over a long period

The relationship of chronic pyelonephritis and hypertension is particularly important In an informative study[42] of chronic pyelonephritis Raaschou has summarized the causes of death in chronic pyelonephritis and surprisingly enough in only 15 0 per cent of his entire post-mortem series did the patients die of various sequelae to arterial hypertension It is emphasized in the study that because of vague symptoms insidious course, and because clinicians do not have the entity sufficiently in mind there is frequently a failure to diagnose the disease correctly

Treatment of Pyelonephritis The steps usually taken in the management of patients who presented themselves with pyelonephritis were the foll

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[41] Weiss and Parker Loc cit p 507

[42] Raaschou Studies of Chronic Pyelonephritis, Copenhagen Ejnar Munksgaard, p 57, 1948

sive kidney function tests were not done, although in the future greater effort should be made to find those cases that are obviously overlooked.[21] In most instar

ism present.

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assumed that

some type of prophylactic agent was used either continuously or at definite intervals Response to treatment was usually prompt unless the patient had overwhelming infection or obstructing lesions Any such obstructing lesion was relieved by surgery as soon as feasible.

Cystitis.—The diagnosis of cystitis in the absence of renal infection has been much less *frequently made in recent years than formerly. This is* in keeping with the statement, frequently made, that in the presence of the triad of frequent urination, dysuria and pyuria, the diagnosis of simple cystitis was seldom substantiated. Today, careful search for the underlying disease will frequently prevent progression to a stage where surgery or other treatment may be necessary.

The diagnosis of cystitis has been made in our diabetic patients chiefly in females in the seventh decade of life and with diabetes of an average duration of 12 years. Severe cystitis with necrosis of large areas in the bladder associated with mixed infection, and actually vesicovaginal fistulæ have occurred rarely In the remaining cases, causes were unknown in some cases of cystitis. Catheterization without adequate prophylaxia has been incriminated But frequently cachexia, urethral prolapse, vaginal and uterine infection have been contributing factors. Treatment was in no way different from pyelonephritis, except that in general, studies were less extensive and treatment more simple

C URINARY TRACT CALCULI

Urinary tract calculi rarely caused urinary tract infection in our group There were 44 patients, 25 males and 19 females, ranging in age from 32 years to 76 years with diabetes of 1 to 27 years duration The average insulin dosage was *18 units In 31 instances stones were located in the* kidney pelves and in 10 instances in a ureter There were 3 cases of bladder stones Six nephrolithotomies, 4 uretherostomies, and 3 nephrectomies were done In six instances it was possible to remove the stone by instrumentation Case 12149, aged 74, with diabetes of seventeen years duration had an operation for carcinoma of the bladder in 1940 Bladder calculi were removed in 1940, 1944, and 1947 Sodium acid phosphate was used in an effort to avoid reformation of stones without avail. He had a chronic Proteus vulgaris and Streptococcus fecalis urinary tract infection that was never eradicated Death occurred April 25, 1950

In the 44 cases there were 25 instances of pyelonephritis. Calcium and phosphorous determinations were done on all but 2 patients and no abnormal levels were found Uric acid stones occurred in one woman Removal of ten stones from the left ureter was successful, and she returned in 3 years with another calculus, renal infection and required left nephrectomy.

[21] Baldwin and Root Loc cit, p 507

D. PERINEPHRIC AND CORTICAL ABSCESS

Perinephric abscesses have been uncommon despite the frequency of urinary tract infection with the predisposition to their development From December 1, 1945, to January 1, 1956, there were 10 cases of perinephric abscess, 9 in females Case 33704, was admitted to the hospital in diabetic coma and with a urinary tract infection. She had been treated elsewhere for a period of two weeks with antibiotics, fluids, and insulin but had steadily grown worse She died on the day of admission to the hospital At post-mortem necrotizing pyelonephritis and a perinephric abscess were found

E DISEASES OF THE PROSTATE

Benign Prostatic Hypertrophy —From December 1, 1945, to September 30, 1957, 153 patients with diabetes and benign prostatic hypertrophy were treated at the George F Baker Clinic with operations equally divided between suprapubic and trans-urethral resections

Complications were numerous in the group as evidenced by the additional diagnoses of prostatitis (13), partial retention (10), carcinoma (8), hypertensive heart disease with failure (4), myocardial infarction (3), nephrolithiasis (2), together with a variety of other complaints. Arteriosclerosis to slight or severe degree was a universal finding However, retinal hemorrhages were recorded in only 3 instances Kidney function as shown by the non-protein nitrogen was satisfactory (40 or below) in 62 cases In only 3 instances was severe vascular kidney disease present There were 12 deaths in the group due to the following, carcinoma 7, hypertensive arteriosclerotic disease 5

Advances in the treatment of surgical cases have encouraged procedures on patients that one would not have tried a decade ago[*] The use of fluids, blood, measurement of electrolytes, control of distention with intubation, management of post operative phlebitis, appreciation of dangers of malnutrition, control of the effects or prevention of postoperative phlebitis,

function was poor enough in 14 instances to produce elevation of the non-protein nitrogen to 45 mg per cent or above In one instance the non-protein nitrogen was 130 mg per cent In general, therefore the patients were poor operative risks

Preoperative preparation was often prolonged particularly in those patients requiring vasectomies or in those with retention, elevated non-protein nitrogen, cardiac failure, severe urinary tract infection, and in those requiring a two stage operation Postoperative complications were few except for urinary tract infection One patient who had a transurethral resection had a secondary fulguration for postoperative hemorrhage but did well thereafter There was only one death in the first postoperative

[*] Harvey Bull New York Acad Med 27 538, 1950

year in which the urinary tract was the primary cause. Death was due to pyelonephritis, hydronephrosis, and hydroureter. Six other patients died in the first post-operative year from cardiovascular disease (4) and carcinoma (2). Postoperative results were in general good. Eighteen patients found it necessary to be followed or treated by oral medication to control or prevent exacerbation of urinary tract infection. In 5 additional patients moderate bladder symptoms continued

Carcinoma of the Prostate.—There were 15 cases treated for carcinoma of the prostate 12 of whom had combined orchiectomy and diethylstilbestrol therapy Their ... diabetic duration eleven years, and ... felt that better results are obtaine... by following up endocrine control months later by surgery, according to Nesbit and Baum

Infection of the Prostate.—From December 1, 1945, to January 1, 1956, prostatitis was diagnosed on 25 occasions. The ages of these patients ranged from 28 to 53 years, average diabetic duration 9 years, and average insulin dosage 26 units. The prostatitis in these instances was non-specific and not accompanied by benign prostatic hypertrophy or tumor. There were two instances of the typical acute prostatic abscess with sepsis in this group

Treatment consisted of penicillin, aureomycin, or one of the sulfonamides In a few instances, when the infection was low grade or chronic, massage was used as an adjunct to the above agents. Results were considered satisfactory in each instance

F PARESIS OF THE BLADDER

Paresis of the bladder is occasionally seen in diabetes. It is associated with diabetic neuropathy with such additional manifestations as areflexia, paresthesiae, hyperalgesia, and hypoasthesia of the extremities, nocturnal diarrhea or enteric neuropathy, orthostatic hypotension, and almost always uncontrolled diabetes of marked degree for months or years Residual urine may be as high as 1000 cubic centimeters and rarely is below several hundred cubic centimeters

[illegible]

poor control, diabetic neuropathy, and vascular lesions.

Treatment consisted of great ... eradication of infection (urinary ... form of vitamins, and persiste... evidence of improvement in all phases of the neuropathy In 10 cases no improvement was noted It was the experience however, that improvement is slow and may actually extend over a period of many years. Surgical ...

...atment of

[65] Nesbit and Baum Jour Am Med Assn, *143*, 1317, 1950
[66] Rundles Medicine, *24*, 111, 1945

G. MISCELLANEOUS

Calcification of the Vas Deferens.—This relatively specific degenerative complication of diabetes has been reported by Marks and Ham[67] in 9 cases and later by Wilson and Marks[68] in 60 cases, of whom 56 were diabetic. Previously reported cases of calcification in either seminal vesicles or the vas deferens numbered forty. The 56 diabetics seen at the New England Deaconess Hospital had acquired diabetes at an average age of 33 4 years and calcification was first noted by x-ray after an average duration of 18 3 years. Arterial calcification (53 cases), retinitis (37 cases), hypertension (24 cases), and proteinuria (27 cases) were co-existing features. The calcification occurred most frequently in the pelvic portions of the vasa and medial to the ureters

Tumors.—The dominant genito-urinary tract tumor was seen in the prostate in the form of benign hypertrophy However, a number of tumors were seen aside from those of the prostate Seven patients were operated for bladder wall tumors Two solitary cysts of the kidney were seen Case [illegible]

no recurrence Case 5488, male, aged seventy-nine, with diabetes of twenty-one years duration had electrocoagulation and radium implantation of a carcinoma of the bladder wall Postoperatively the patient developed thrombophlebitis and septicemia At postmortem he was found to have necrotizing renal papillitis, carcinoma of the prostate, bronchopneumonia, and a polyp of the rectum Case 31481, female, aged fifty-nine, had an inoperable malignancy of the kidney Case 3654, male, aged eighty, had a highly malignant carcinoma excised from the bladder wall in 1944 He was operated for a recurrnece in 1949 and died of the carcinoma in January 1950 (See Chapter 24)

Malformations.—Case 28795, female, aged fifty-five, with diabetes of twelve years duration, had a hypoplastic left kidney without decrease in function. Case 10769, female, aged nineteen, with diabetes of sixteen years duration and an insulin dosage of 72 units had an ectopic right kidney lying anterior to the second lumbar vertebra Nine cases of undescended testes were seen There were a variety of minor disorders including hydroceles, varicoceles, urethroceles, and disorders of micturition of congenital origin

Other Conditions.—The liability to infection has made phimosis a fairly frequent problem Nineteen patients were seen with this condition and doubtless there were others Eleven patients had local infection as a result of phimosis Twelve patients had circumcision It would seem from the incidence of infection that any patient with phimosis and diabetes should be operated on if his general status permits

Case 23807, aged forty-nine, with diabetes of eight years duration had both Peyronis' disease and Dupuytren's Contracture

[67] Marks and Ham Am Jour Roent Rad Ther , 47, 859, 1942
[68] Wilson and Marks New England Jour Med , 245, 321, 1951

year in which the urinary tract was the primary cause. Death was due to pyelonephritis, hydronephrosis, and hydroureter. Six other patients died in the first post-operative year from cardiovascular disease (4) and carcinoma (2). Postoperative results were in general good Eighteen patients found it necessary to be followed or treated by oral medication to control or prevent exacerbation of urinary tract infection. In 5 additional patients moderate bladder symptoms continued.

Carcinoma of the Prostate.—There were 15 cases treated for carcinoma of the prostate 12 of whom had combined orchiectomy and diethylstilbestrol therapy. Their ages averaged seventy years, diabetic duration eleven years, and average insulin dosage 18 units. It is felt that better results are obtained by combined initial therapy[65] than by following up endocrine control months later by surgery, according to Nesbit and Baum.

Infection of the Prostate.—From December 1, 1945, to January 1, [illegible]

were two instances of the typical acute prostatic abscess with sepsis in this group.

Treatment consisted of penicillin, aureomycin, or one of the sulfonamides. *In a few instances, when the infection was low grade or chronic, massage* was used as an adjunct to the above agents. Results were considered satisfactory in each instance.

F PARESIS OF THE BLADDER

Paresis of the bladder is occasionally seen in diabetes. It is associated with diabetic neuropathy with such additional manifestations as areflexia, paresthesiae, hyperalgesia, and hypoasthesia of the extremities, nocturnal diarrhea or enteric neuropathy, orthostatic hypotension, and almost always uncontrolled diabetes of marked degree for months or years Residual urine may be as high as 1000 cubic centimeters and rarely is below several hundred cubic centimeters

The striking finding in this group other than the history of poor diabetic control is the great number of complicating vascular lesions, infections, and other degenerative changes Rundles[66] has called attention to the associated poor control, diabetic neuropathy, and vascular lesions.

Treatment consisted of great effort for extended good diabetic control, eradication of infection (urinary tract and elsewhere), supportive care in the form of vitamins, and persistent follow up. In 17 instances there was evidence of improvement in all phases of the neuropathy In 10 cases no improvement was noted It was the experience however, that improvement is slow and may actually extend over a period of many years. Surgical resection of the bladder neck has given relief in selected cases

Certainly no treatment thus far used has been effective in the treatment of diabetic neuropathy without concomitant good control of the diabetes

[65] Nesbit and Baum Jour Am Med Assn, *143*, 1317, 1950
[66] Rundles Medicine, *24*, 111, 1945

organisms from the colon must be avoided Female patients should be instructed to cleanse toward the anus and not toward the vagina, as has

In Case 2568, housewife,

ith acute moniliasis of the

effective. The common

infections, although frequently

commonly found in the colon

tic, should be performed with

aseptic conditions Whenever a retention catheter is necessary, prophylactic chemotherapy may be given Obstructive or static abnormalities of the urinary tract should be corrected.

In the management of pyuria the following principles of management should be closely observed. The first essential is to keep the urine sugar free throughout the entire 24 hours This is a *sine qua non*

1 The physician who sees a patient with early urinary tract infection has the best chance of eradicating that infection before the development of complicating features

2 Identification of the organism and laboratory tests for sensitivity to streptomycin, aureomycin, penicillin and terramycin or other antibiotics make selection of the proper agent for treatment more assured This course in the diabetic is the most economical one in many instances

3 In addition to treatment a thorough search should be made for the cause of infection Pyuria is usually cleared up without difficulty Without eradication or correction of the fundamental exciting cause, recurrence and extension of infection is the rule

4 Prompt investigation is essential Delay often results in destructive

1

be controlled by one agent, only to be replaced by another smoldering organism of equal virulence that is not controlled without a change in treatment

6 Bladder distention in the comatose, aged, and postoperative patients should be avoided (*a*) by requiring a daily record of the 24 hour urine excretion in every diabetic in the hospital

(*b*) Investigation of changes in daily output

(*c*) Repeated examination of the urine, both microscopic and chemical, at regular intervals.

7 The catheter should be used readily if needed but its use should be followed by prophylactic doses of an antibiotic, or a sulfonamide, sulfadiazine, or Gantrisin, to prevent infection Two grams of the drug daily for 3 or 4 days with adequate fluid to insure an output of 1500 cc of urine daily will usually prevent infection If an indwelling catheter is necessary small doses of the sulfonamide daily may be used

8 *Urinary tract infection in the diabetic demands follow-up treatment for an extended period*

Pneumaturia.—Primary pneumaturia, occurring in the absence of in-

obstruction was present in one. If pneumaturia has occurred the urine may

in a 26 year old diabetic patient admitted to the Peter Bent Brigham Hospital on the seventh day of anuria. Two months after delivery of a stillborn infant she developed diabetic acidosis. A few days later she became anuric. On the 18th day of anuria she underwent dialysis with the Kolff-Brigham artificial kidney. On the 23rd day the urine output rose to 615 cc. and she entered the diuretic phase. Recovery was slow but five months later she was in renal balance with a normal non-protein nitrogen level in the blood. The etiology of bilateral cortical necrosis in this case was not clear.

Treatment of Anuria.—Excluding the anuria which may occur as a terminal event in chronic renal disease, acute renal shut-down has occurred in our diabetic patients most frequently as a sequel to diabetic ketosis (see page 371) or as a complication of renal infection. Under these circumstances the patient is unable to take food or liquid by mouth. Constant intravenous administration of glucose solution, 20 to 40 per cent, in water at a rate of 750 cc. to 1200 cc. per 24 hours has been employed. The amount selected has been based on a consideration of the insensible perspiration which varies with total metabolism plus any liquid lost by vomiting or as urine in case of oliguria. Repeated observations of the serum electrolytes is necessary. Hyperkalemia is especially to be feared but has, in our cases, not proved a problem since most commonly, the diabetic patient is already suffering from hypokalemia through loss of potassium during the phase of ketosis or uncontrolled diabetes.

II. PRINCIPLES OF MANAGEMENT

Prophylaxis.—Prevention of urinary tract infection should begin with the early detection of diabetes and prompt initiation of adequate treatment before excessive hyperglycemia and ketosis have occurred. When an adequate diet has been normally utilized with the aid of insulin, the urine will become sugar free, pruritus and local irritation will cease, unless infection has already occurred.

, should be taught. The
ents, together with the
ig due to pruritus, are
genuine dangers. Contamination of vulvae and the urethral orifice with

[69] Foord, Nabarro and Riches: Brit. Med. Jour., *1*, 433, 1956.
[70] Boucot, Guild and Merrill: New England Jour. Med., *257*, 416, 1957.

pruritus ani in diabetes, as well as certain cutaneous eruptions, as due to vitamin deficiencies, especially of nicotinic acid as seen in pellagra, we have not been impressed in our patients by evidence that vitamin deficiencies are responsible for these conditions

The diabetic skin would appear to be more easily infected with monilia than the nondiabetic. Dermatologists seeing our patients have stated that monilia infection in diabetics is primarily of the vulvar mucous membranes with possible extension to the skin, whereas in nondiabetics monilia infections are more ofte[illegible]
groins and axillae. [illegible]
examined the urine [illegible]
incidence of yeasts potentially pathogenic for man They found that the urine of 34 7 per cent of 150 diabetics with glycosuria contained yeasts as contrasted with only 8 per cent of 50 diabetics who were aglycosuric The latter figure was essentially the same as that (10 per cent) for 100 nondiabetics without sugar in the urine In other words, it was the sugar in the urine rather than the diabetes *per se* which apparently made the difference. The yeasts isolated were all species of Candida ("Monilia") and chiefly of the Albicans variety In both diabetic and nondiabetic patients, yeasts occurred much more commonly in female than in male patients Mehnert and Mehnert stress the importance of strict control of diabetes in the prevention and treatment of vaginitis or other urogenital infections due to Candida.

Epidermophytosis.—Behrman and Levin[4] found dermatophytosis of the feet to be the most common skin disease in diabetic patients with a much greater incidence than in nondiabetic individuals Likewise epidermophytosis was the most common disease in diabetic patients studied by Greenwood[5] In his series, including all types, there were 198 cases, or 40 per cent of the entire group of 500 individuals, in which this was present in the feet Eve [illegible]
of the feet [illegible]
than for [illegible]
fections may be more serious They give to the skin a parboiled appearance between the toes with, at times, open fissures in the depths of the inter- [illegible]

serious infections Many a diabetic patient has subsequently lost a toe or a foot resulting from osteomyelitis in which the original infection came about because of epidermophytosis

There is danger in treating epidermophytosis with strong proprietary preparations of unknown composition It is probably true that at least half of the cases seen by dermatologists show severe dermatitis due to such treatment and quickly subside under the simplest methods, such as boric acid soaks and compresses and bland applications In addition, too vigorous treatment of fungus infections is at times followed by a generalized

[3] Mehnert and Mehnert Diabetes, 7, 293, 1958
[4] Behrman and Levin Jour Mt Sinai Hosp, 13, 257, 1947
[5] Greenwood Jour Am Med Assn, 89, 774, 1927

Chapter 20

DISORDERS OF THE SKIN IN DIABETES

Alexander Marble, M.D.

Introduction.—Although there are no diseases of the skin which are absolutely unique to diabetes, certain affections are more common in diabetics than nondiabetics. Among these are infections with furuncles, boils and carbuncles, formerly more common than now, pruritus of the external genitalia seen particularly in female patients with marked glycosuria, *xanthosis, xanthomata and necrobiosis lipoidica. Epidermophytosis has* been thought by some to be more common in diabetic than in nondiabetic persons. In addition to these, there are in treated patients the untoward effects of insulin including allergic responses (see Chapter 14), and the lipodystrophies.

There is no direct evidence that hyperglycemia *per se* predisposes to disease of the skin. As far as infections are concerned, experiments *in vitro* have shown that blood to which 0.5 to 1 per cent dextrose has been added is no better culture medium for staphylococci than normal blood and that adding dextrose does not diminish the blood's bactericidal power. For further discussion see page 454. However, the conditions named in the preceding paragraph are so commonly encountered in diabetes that their occurrence should suggest the presence of this disease.

Urbach[1] maintained that there was a condition which he called "skin [illegible] eczema and [illegible] t [illegible] insulin.

Pruritus.—Pruritus pudendi frequently occurs in uncontrolled diabetes *especially in females. If it does not vanish within a few days after the* [illegible] usually disclose a [illegible] incontinence, [illegible], or urticaria [illegible] As for non- [illegible] ches and the simplest ointment may be helpful. The use of oil on the skin or mucous membranes to prevent irritation during micturition is *helpful. Mild sedatives* with or without aspirin, often may be of value to overcome nervousness and fatigue due to the disturbance of sleep because of the itching.

Although Rudy and Hoffmann[2] regarded vulvitis, pruritus vulvæ, and

[1] Urbach: Jour. Am. Med. Assn., *129*, 441, 1945. See also Urbach: Skin Diseases, Nutrition and Metabolism, New York, Grune and Stratton, 1946.
[2] Rudy and Hoffmann: New England Jour. Med., *227*, 893, 1942.

fected neighboring tissue Treatment with appropriate doses of antibiotics is of great value. It goes without saying that careful control of the diabetic condition is imperative

Formerly the carbuncle was one of the most serious complications seen in diabetics and even today deserves most careful respect and attention However, with this as with other infections in the diabetic, antibiotics have conferred a great blessing and have altered the plan of treatment radically For further discussion, see page 597.

Xanthosis.—Xanthosis or xanthochromia is a yellowish discoloration of the skin seen at times in diabetic patients It is noticeable particularly on the palms of the hands, soles of the feet and on the nasolabial folds It is accompanied by an increase in the carotene content of the blood and often of the cholesterol content as well It is due to a disturbance in the patient's ability to metabolize carotene, a lipochrome found in large amounts in green and yellow vegetables, egg yolk and butter Xanthochromia is not confined to diabetics Boeck and Yater[6] observed it in 9 per cent of 100 patients with diabetes, in 9 per cent of 22 patients with renal disease and in 3 per cent of 23 other hospital patients selected at random

Treatment consists in adequate control of the diabetic condition, temporary restriction of the intake of carotene-rich foods and supplementary medication with vitamins and minerals as indicated to replace those ordinarily supplied by the foods restricted The patient may be reassured regarding the condition since, except for the cosmetic effect, xanthochromia is not of importance and causes no symptoms

Xanthoma Diabeticorum—A now uncommon skin condition in diabetic patients is that of xanthoma diabeticorum in which are seen scattered bright red nodules mottled with a deep rose tint The individual lesions vary in size, some having a diameter as great as 5 mm The lesions are most numerous on the outside and back of the forearms and especially about the elbows and knees In patients with diabetes they are associated with an increase in the total lipid and cholesterol content of the blood to which they are secondary Treatment consists of careful control of the diabetic condition so as to bring about lowering of blood lipid and cholesterol values When this is accomplished by means of diet and insulin, the lesions disappear[7]

Somewhat similar xanthomatous lesions, xanthoma tuberosa and xanthoma plana, occur as evidence of a systemic disease, primary xanthomatosis, in which not only the skin but also the viscera are involved Xanthoma tuberosa and xanthoma plana are associated with an increase in cholesterol total fat and [illegible]

xanthomatous conditions

[6] Boeck and Yater Jour Lab and Clin Med, *14*, 1129, 1929
[7] Gumpel and Lipton A M A Arch Int Med, *96* 560, 1955
[8] Montgomery and Osterberg Arch Dermat and Syph, 37, 373, 1938
[9] Thannhauser and Magendantz Ann Int Med, *11*, 1662, 1938

eruption, an epidermophytid
tion should not be treated
ticularly to the hands wher
elsewhere are most frequent.

The prevention of epidermophytosis consists in not walking with bare feet particularly on floors where the fungus often is present such as in gymnasiums, showers, swimming pools and at home where other members of the family are infected.

In the treatment of moist or vesicular lesions, the feet may be soaked in a solution of 1:4000 solution of potassium permanganate or 1 per cent aqueous solution of aluminum acetate for one-half hour daily. For less acute conditions, one may apply nightly ointments such as half-strength Whitfield's ointment, those containing undecylenic acid (Desenex* Ointment) or one such as the following which we have found particularly useful:

Precipitated sulphur	2 gm
Salicylic acid	2 gm
Petrolatum	30 gm
Mix	

Once control has been gained of the acute condition, exacerbations may
thorough drying
between the toes
suitable powder is
the following:

Salicylic acid	2 gm
Benzoic acid	2 gm
Talc	100 gm
Mix	

Infections of the Skin.—Infections of the skin demand immediate, thorough and yet gentle treament. One of the first duties of the physician *is to tell diabetic patients to keep the skin clean and to report the beginning* of an infection at once. Patients should be warned of the danger from slight wounds, should specifically be advised to avoid tissue injury with bleeding in the cutting of nails, corns and calluses, and to report promptly any

hand if the skin of the feet is too soft and tender, the daily use of alcohol rather than lanolin is indicated.

be gently cleansed with soap and water daily, followed by alcohol and blotting the skin dry rather than rubbing so as to avoid contaminating unin-

sone ointment and to injections of hydrocortisone into the lesions. From preliminary observations Hoet[16] has the impression that in some cases the giving of Vitamin A may be helpful. The diabetic condition should be controlled carefully and standard local treatment of the lesions provided if they become ulcerated or secondarily infected.

As summarized by Ormsby and Montgomery,[17] the lesions histologically show necrobiotic rather than true necrotic changes in the collagen fibers. There are homogenization and degeneration of the collagen fibers together with loss of elastic tissue and a peripheral perivascular inflammatory reaction involving chiefly connective tissue cells, various types of histiocytes, lymphocytes and occasional leukocytes and plasma cells. Varying degrees of obliterative changes are seen in the smaller blood vessels which are surrounded by an infiltrate, thus accounting for the necrobiotic changes [illegible]

Dermatitis Gangrenosa.—Gangrene of the skin of the trunk or arms [illegible]

resistance was lowered by acidosis. One such case occurred at the New England Deaconess Hospital when a coma patient developed a gangrenous slough at the site of a hypodermic injection.

Dupuytren's Contracture.—We have noted that contraction of the palmar fascia seems to occur more frequently among older diabetic, than non-diabetic, persons. This has also been Wilder's[19] impression. Schneider[20] found that 120 of 381 patients in a diabetes clinic had Dupuytren's contracture. He regards the condition as reversible and discusses various possible etiologic factors. A complete bibliography is given. Although [illegible]

the advent of insulin, it gradually disappeared and one never sees it today except in neglected cases and diabetic pseudodwarfs.

Lipodystrophy.[21]—Not long after the introduction of insulin it was reported by various observers that certain patients developed changes in subcutaneous fat at the site of injections.[21] These at times took the form of hypertrophy and at times of atrophy. Both types of change might appear in the same individual either concurrently or in succession. Early work showed the changes in adipose tissue were probably not related

[16] Hoet. Personal communication.
[17] Ormsby and Montgomery. Diseases of the Skin, 8th ed., Philadelphia, Lea & Febiger, p. 756, 1954.
[18] Riven. Am. Jour. Med. Sci., *189*, 550, 1935.
[19] Wilder. P. 299, Loc. cit., p. 71.
[20] Schneider. Medicine in So. Africa, 96, 1957.
[21] Marble and Renold. Trans. Assn. Am. Physicians, *62*, 219, 1949.

Xanthelasma.—*Xanthelasma* consists of collections of slightly raised, [illegible]

page 557.

Necrobiosis Lipoidica Diabeticorum.—In 1928, Oppenheim[10] observed a hitherto undescribed skin condition in a diabetic patient. In 1932, Urbach[11] reported the study of a similar lesion to which he gave the name of necrobiosis lipoidica diabeticorum. The tendency now is to omit the term "diabeticorum" since about *10 per cent of cases occur in nondiabetics* However, as Cannon[12] pointed out, necrobiosis lipoidica may be found months or years prior to the onset of diabetes. Likewise, Hildebrand, Montgomery and Rynearson[13] reported that in 18 per cent of a series of 86 [illegible] years [illegible] ses [illegible] ny eventually appear.

In this condition the earliest lesions are elevated with papules from 1 to 3 mm. in diameter with sharply outlined borders. They may be capped by a slight scale and do not disappear under pressure. In later stages the lesions take the form of round, oval or irregularly shaped plaques with well-defined borders having a firm consistency and glistening surface which appears somewhat as if it were covered with a layer of tightly stretched cellophane Still later, there may occur a circular area of depression with atrophy and ulceration. With care to prevent secondary infection, almost invariably the shallow ulcerations eventually fill in leaving a thin layer of scar tissue

Necrobiosis lipoidica is stated to occur 4 times as frequently in the female as in the male However, in our own series among a total of 37 cases of necrobiosis lipoidica in patients with onset of diabetes at the age of fifteen years or under and with duration of diabetes fifteen years or over, the distribution between the sexes was about equal, 19 males and 18 females In some patients a history of injury may be obtained The lesions may be single or multiple and they occur most often on the lower legs or about the ankles although they may be found on the thighs, arms, hands, abdomen and back At times surprisingly symmetrical lesions may occur on the two legs The condition of any individual lesion may often remain stationary for months or years In the case reported by Goldberg and Rosenberg,[14] *necrobiosis lipoidica was observed in a patient with intercapillary glomerulosclerosis*

The etiology of this peculiar skin condition is unknown, as possible causes [illegible]

[10] Oppenheim Zentr f Haut u Geschl, *12*, 179, 1929-30
[11] Urbach and Retpo Arch f Dermatol, *166*, 273, 1932
[12] Cannon South Med Jour, *38*, 105, 1945
[13] Hildebrand, Montgomery and Rynearson Arch Int Med, *66*, 851, 1940
[14] Goldberg and Rosenberg A M A Arch Dermat, *71*, 642, 1955.
[15] Savitt *Ibid*, *506*, 1955

is neutral fat; (2) the abnormal process consists almost exclusively of simple disappearance of fat with little, if any, evidence of inflammatory reaction, (3) insulin lipodystrophies follow in susceptible persons the administration of any variety of insulin, (4) the reaction of the insulin is not an important factor since atrophies follow the use of insulins with a pH at or near neutrality as well as those acid in reaction.[23]

Other work in our laboratory[24] has shown that adipose tissue from human patients obtained at operations exhibits definite lipolytic activity and that there is a definite sex difference with activity considerably greater in females. In view of the greater incidence of atrophies among adult females, these findings concerning lipolytic activity were regarded of as likely significance but it was not possible to demonstrate their actual bearing on the problem. Consequently, attention was turned to a study of the local effects of insulin in animals. Knowing of the favoring influence of insulin on glycogen deposition in the subcutaneous fat of normal animals,[25] [26] it was considered pertinent to determine the effect of insulin in this regard *at the site of injection* and at the same time to observe any tendency to increase or decrease of fat locally after prolonged injections.

Female rats were injected daily for 2 months into the groin fat pads, using 5 units of protamine zinc insulin on one side and isotonic salt solution on the other. It was found that not atrophy but hypertrophy of the fat developed on the side receiving insulin when compared with the control side. That this hypertrophy represented a real increase in fat was shown by an increase in the total amount of lipid present. Furthermore, on histological examination it was noted that a definite increase in the size of individual fat cells had occurred.[27] This experience in rats and certain observations in patients suggest that the primary response to repeated injections of insulin in a given area may be hypertrophy and that atrophy may follow later by a mechanism which at present is not entirely clear.

Wertheimer[28] and Fawcett[29] found that the administration of insulin to rats led to the deposition of glycogen in subcutaneous fat. Our own studies included diabetic as well as normal rats and indicated that the amount of glycogen deposited was particularly great in the diabetic animals. Furthermore, it was shown that this action of insulin was local as well as general since a distinctly greater deposition of glycogen occurred at the site of injection than elsewhere.

The demonstration of this double local action of insulin, deposition of glycogen and hypertrophy of the adipose tissue, added to the substantial evidence which has accumulated recently,[30] [31] [32] strongly suggests that the adipose tissue cell itself can synthesize fatty acids from carbohydrate. It therefore seems justifiable to conclude that the primary action of insulin

[23] Marble and Smith. Loc cit p 526
[24] Renold and Marble. Jour Biol Chem, *185*, 367, 1950
[25] Wertheimer. Jour Physiol, *103*, 359, 1945
[26] Fawcett. Endocrin, *42*, 454, 1948
[27] Renold, Marble, and Fawcett. Ibid, *46*, 55, 1950
[28] Wertheimer. Loc cit p 527
[29] Fawcett. Loc cit p 527
[30] Fawcett. Loc cit p 527
[31] Renold, Marble and Fawcett. Loc cit p 527
[32] Wertheimer and Shapiro. Physiol Reviews, *28*, 451, 1948

to preservatives (such as tricresol) in the *product, to the presence of a* lipase in market insulin, to inflammatory responses, to the mechanical trauma of injection or to traces of alcohol which might be left in the syringe [illegible]

of their greater importance from a cosmetic standpoint. In a survey of 1096 consecutive diabetic patients of all ages who had taken insulin for *one year or longer*, 24.2 per cent showed atrophies to a greater or less degree (see Table 90). However, in the 312 patients in the series who were under

TABLE 90.—INCIDENCE OF INSULIN ATROPHIES IN 1096 PATIENTS WHO HAD RECEIVED INSULIN FOR ONE YEAR OR MORE

Sex and Age Groups	*Total Patients No*	*Atrophies No*	*Atrophies Per Cent*
Males			
Under 20 years	169	67	39 6
20 years and over	271	9	3 3
Females			
Under 20 years	173	85	49 1
20 years and over	483	104	21 5
Both Sexes			
Under 20 years	312	152	44 4
20 years and over	754	113	14 9
All ages	1096	265	24 2

the age of twenty years, atrophies occurred in 44 4 per cent as contrasted with an incidence of only 14 9 per cent in the 754 patients twenty years of age or older. In patients under twenty, atrophies were only slightly more common in females than in males, whereas in those twenty and over the incidence among females was almost 7 times as great. Actually in the adult male group, only 3 3 per cent showed atrophies This extraordinary sex difference appears to be real although it must be admitted the layer of subcutaneous fat available for change is often less in adult males than in adult females

The difference in incidence between the sexes is present also as regards hypertrophies but this abnormality is more common in males. Thus among 596 diabetic patients of whom 259 were males and 337 females, hypertrophies occurred in 39 3 per cent of males under the age of 20 years as contrasted with only 17 9 per cent among females Among patients aged twenty and over, hypertrophies were found in 20 5 per cent of males and in 11 7 per cent of females Once again it must be admitted that the sex difference may be related to a thicker layer of subcutaneous fat in the female, making observations and interpretations of slight changes more difficult

Apart from the influence of age and sex, in our Clinic studies have shown the following (1) in insulin atrophies the type of tissue which disappears

ⁿ Marble and Smith Proc Am Diabetes Assn , *2*, 137, 1942

Chapter 21

DISEASES OF THE BLOOD

HOWARD F ROOT, M.D

DURING the observation of diabetic patients over a period of years, a variety of blood disorders occur, which are either intercurrent, independent complications, or are dependent, wholly or in part, upon common clinical features of diabetes Among such factors may be mentioned the acute and chronic infections, the diabetic nephropathy, deficiency of pancreatic enzymes, and finally, genic factors If the circulating blood and the blood-forming organs are to be regarded as a single organ, the erythron,[1] susceptible to many influences, metabolic, infectious, toxic or neoplastic, then one might expect to find a relative preponderance of certain types of blood disease in diabetic patients Thus, abnormalities of corpuscular composition, especially the anemias, are of frequent occurrence, whereas disorders of coagulating ability, "prothrombin deficiency and hemophilia," and lesions of the small blood vessels "purpuras" seem no more frequent than in non-diabetics

A ANEMIA

Anemias, due to loss of erythrocytes, may be caused by conditions which are acute or recurrent The common causes for such acute anemias have been hemorrhage from peptic ulcer, chiefly duodenal, from bleeding esophageal veins in cirrhosis of the liver, carcinoma of the stomach, or intestinal tract, or malignant lesions of the genito-urinary tract In one instance severe hemorrhage from a duodenal ulcer was associated with the onset of diabetic coma in a man with a previously unrecognized ulcer In two other instances, severe hemorrhage and shock associated with cirrhosis of the liver in one and duodenal ulcer in the other, produced unconsciousness with rapid pulse and respiration, which was confused with diabetic coma However, the moist skin and firm eyeballs in each, together with blood and urine tests, served to facilitate the diagnosis In such cases with sudden and severe hemorrhage, shock is manifest by pallor, sweating, restlessness, tachycardia and low blood pressure with greatly reduced blood volume Tissue fluids gradually restore the volume of blood, but this results in a dilution of red cell and hemoglobin concentration for a day or two The treatment of acute blood loss is treatment of shock, by control of hemorrhage appropriate to the cause and prompt restoration of blood volume Transfusions of whole blood are most effective

[1] Boycott Pathology of the Blood In, Chap II, Textbook of General Pathology, New York Pembrey and Ritchie, 1913

at the site of injection is a direct metabolic one, facilitating the synthesis of fat from carbohydrate
sponse of adipose tissue.
tissue was not altered by
of time.

From a study of patients with unstable diabetes, six with insulin atrophies and three with hypertrophies, Paley and Scott[32a] concluded that lipodystr

lip

and further work is necessary. Meanwhile the following suggestions to patients may be of help: (1) in making the injection, deposit the insulin beneath or at least in the lower layers of the subcutaneous fat and not superficially, (2) constantly shift the site of injection so that no one area of 2 cm in diameter receives insulin oftener than once every 3 or 4 weeks; (3) if known to be susceptible to atrophies, avoid the arms and legs for injections and use those parts of the body not exposed to public view such as the abdominal wall, flanks and buttocks If despite all precautions, atrophies do occur, patients may be reassured as to the benign character of the condition The chief disadvantage is cosmetic Only the fat and

injections, gradual restitution of subcutaneous fat takes place over many months

Three other ideas regarding prevention and treatment of insulin atrophies deserve mention (1) Insulin may be given intramuscularly, avoiding the subcutaneous tissues However, patients often dislike the longer needle and the deeper injection which are necessary Duncan[33] suggests that the tendency to disappearance of subcutaneous fat may be less if cold insulin is not injected Consequently he recommends that insulin not be kept in the refrigerator just prior to use However, although we have often advised patients to keep at room temperature the vial currently in use, we have not noted that this lessened the tendency of insulin atrophies. Collens and co-workers[34] have suggested the continued injection of insulin into the depths of areas of atrophy and states that in his experience the lost subcutaneous fat is gradually restored Günther[35] has reported success with this procedure. H
not too hopeful
injections in an
immediately above muscles with perhaps a large vein coursing through the area

32a Paley and Scott Brit Med Jour, *2*, 1331, 1938
33 Duncan Loc cit, p
34 *Collens, Boas, Zilinsky and Greenwald New England Jour Med*, *241*, 610, 1949
35 Günther Klin Wchnschr *30*, 1080, 1952, Abst Diabetes *4*, 63, 1955

Deficiency of Folic and Ascorbic Acid.—Deficiency of ascorbic acid undoubtedly occurs not rarely in diabetic patients. It may condition a primary deficiency of folic acid because ascorbic acid is required for the conversion of pteroylglutamic acid to the metabolically active form the citrovorum factor or folinic acid. The citrovorum factor has been considered to play a part in the capillary fragility, seen particularly in young diabetic patients, and sometimes thought to be a factor in diabetic retinitis. In measurements of the ascorbic acid content of the blood in diabetic patients at the New England Deaconess Hospital, values below normal were found chiefly in ward patients whose diet had been greatly restricted, particularly in the matter of fruit. They were studied with particular reference to surgical complications and healing.

Deficiency of iron is a common cause of hypochromic anemia. Such conditions are seen in young patients with deficient iron endowment from

diabetic patients, although occasional anemia from exposure to drugs occurs. The diabetic nephropathy which today causes more than 50 per cent of the deaths occurring in young diabetic patients is characterized by renal failure and anemia in the last months or years of life. In addition, such patients have had periods of acute, and finally, chronic pyelonephritis. In order, diabetes, prostatic obstruction or chronic nephritis of vascular type are common causes for renal failure. For severe anemia, transfusions will temporarily improve the comfort of the patient who is suffering from dyspnea and weakness. The use of intravenous iron may be tried.

The anemia associated with nitrogen retention is poorly understood, but marrow studies usually indicate that there is a "toxic" marrow inhibition. Often the degree of anemia does not parallel the degree of nitrogen retention, and the red cell indices are normocytic or microcytic, but never hypochromic. In contrast to this, iron deficiency is usually associated with erythroid hyperplasia of the bone marrow and marked hyperchromia of the cells. The serum iron is usually normal with renal disease and always low with iron deficiency. It has been shown that the bone marrow hemosiderin content is decreased with iron deficiency and normal or increased with uremia. These studies would indicate that with renal insufficiency the body has normal iron stores and the normal red cells are produced, but their rate of production is decreased.

Studies with radioactive iron have indicated that the rate of utilization is depressed roughly proportional to the degree of azotemia. Again these investigators have suggested that there was no fault in iron metabolism, but that the difficulty was due to poor blood production. Few iron absorption studies have been done on these individuals, but those of Carl Moore would suggest that iron absorption is decreased.

Important among the causes for inhibition of erythropoiesis are the chronic infections seen in diabetic patients of older years, this may not be severe, with red blood cell levels of 3 million to 4 million, but it may seriously impair the healing of severely infected feet, especially when the feet have

Anemia, due to increased erythrocyte destruction, has occurred among our diabetic patients in the presence of septicemia or bacteremia, chemical intoxication, and in occasional cases, from intrinsic causes. The streptococcus and staphylococcus bacteremias once fairly frequent among diabetic patients are rarely seen at the New England Deaconess Hospital One case of Welch's bacillus septicemia, associated with extensive gas formation around the kidney, was accompanied by a severe anemia. Anemias from lead and aniline derivatives have not occurred During a period when sulfonilamide was extensively used, a few cases of severe anemia occurred in diabetic patients, particularly in those with treatment of infections of the urinary tract. Recently, one woman developed a severe anemia under treatment with one of the sulfonylureas Her hemoglobin level fell to 8 0 grams during a period of nausea, malaise, loss of appetite and weakness. Recovery was prompt with the use of iron and omission of the drug. In another case, female, age 62 years, use of a sulfonylurea was followed at the end of 4 weeks by jaundice, malaise and hepatitis Within 7 days, an acute hemolytic anemia developed The patient's serum agglutinated her own red cells Sternal puncture revealed a hemolytic anemia At autopsy, severe hepatitis with bile stasis and necrosis of liver cells together with severe renal damage was found Myelophthisic hemolytic anemia occurred in Case 6641 His case was followed for one month by Dr James L Tullis. Eventually, leukemic infiltration of the lungs occurred, and at autopsy, myeloid leukemia was found. Sickle-cell anemia and thalassanemia have not been recognized in our diabetics Acquired hemolytic jaundice as used by Castle[2] has been seen but rarely Its onset has occurred in older diabetic patients without any known familial anemia in association with cirrhosis or carcinomatosis. In one case marked enlargement of the spleen with some enlargement of the liver was present for a number of years Red blood count varied from 2,700,000 to 3,000,000 The use of liver extract, iron and other remedies was ineffective She finally developed hypertension, coronary arteriosclerosis and died of a myocardial infarction

Anemias due to decreased erythrocyte production are classified by Castle[2] according to various causes for "failure of the bone marrow to produce red cells, the hemoglobin to keep pace with the normal rate of red cell destruction" It is clear the great majority of the cases of anemia seen in diabetic patients are secondary Nutritional deficiency, the toxic effects of chronic [illegible] A sample [illegible] it with red [illegible] ous anemia and 10 had only arteriosclerosis and hypertension as complications, but in the group as a whole infections of the urinary tract, tuberculosis and particularly [illegible] tendency [illegible]

Nutriti[illegible] exemplified particularly in the macrocytic anemia associated with deficiency of vitamin B_{12}, folic acid and iron deficiency

[2] Castle In Cecil and Loeb Textbook of Medicine, 9th ed, Philadelphia, Saunders, p 1176, 1955

[3] Mohr Am Jour Med Sci, 196, 67, 1938

suria had been discovered two months prior to admission, but she had never received insulin. The skin had a lemon tint. The tendon reflexes were normal, but vibratory perception was diminished over the malleoli On admission, the blood sugar was 0 312 per cent, the red blood count 2,140,000 per cubic millimeter, the hemoglobin 7 0 grams per cent, and the hematocrit 21 per cent. Gastric aspiration revealed histamine achlorhydria Insulin restored the blood sugar to normal, and on the fourth hospital day

arm The hemoglobin had dropped to 5 3 grams per cent, and the highest reticulocyte response was 5 1 per cent She died on the eleventh hospital

cult

Clinical Features.—Wintrobe[7] states that pernicious anemia is rare

mass in the right lung and anemia Seven years before admission at the age of twenty-six, liver injections had greatly improved an anemia The

vated to 1 3 mgm per cent Bone marrow examination showed a megaloblastic picture characteristic of pernicious anemia At the end of a month the hemoglobin had been raised to 14 8 grams per cent with daily vitamin B_{12} Prior to surgery the patient experienced a severe hemolytic transfusion reaction Because the Coomb's test was positive, ACTH was given A right exploratory thoracotomy and excision of the mass were done without incident or transfusion reaction Fortunately microscopic examination showed the mass to be inflammatory

Spinal cord symptoms were present in 67 of the 168 cases of combined pernicious anemia and diabetes reported in the literature Case 18321, housewife, aged forty-three years at the time of the discovery of diabetes and pernicious anemia in 1942, was unable to stand because of weakness, spasticity and ataxia Recovery from the cord symptoms occurred rapidly after the use of liver extract Later she made a rapid recovery from an acute depression treated by means of electric shock therapy She was alive in May 1958

Diagnosis.—*Clinical Features* In the great majority of known cases, diabetes has preceded the onset of pernicious anemia, and when the classical

[7] Wintrobe Clinical Hematology, Philadelphia, Lea & Febiger, p 435, 1951

B PERNICIOUS ANEMIA

Deficiency of vitamin B_{12} together with the characteristic gastric anacidity and lack of the thermolabile substance (intrinsic factor of Castle) are essential features in pernicious anemia.

Although Addison was the first to describe completely the clinical features of pernicious anemia in 1855, Combe[4] referred to a case in 1823 that undoubtedly was pernicious anemia. There are certain clinical similarities between untreated pernicious anemia and diabetes mellitus. Today it is no problem to differentiate the two diseases. However, in 1823 Combe wrote: "At one time, from the state of his stools and urine, I was led to suspect an affection of the liver; at another, from the thirst, great flow of urine (exceeding the liqud ingested), and the peculiar state of the skin, I was apprehensive of diabetes, but none of these indications remained long stationary."

The co-existence of diabetes mellitus and pernicious anemia was first reported by Parkinson[5] in 1910. The report by Root[6] of 79 cases of perni- ... rity of the literature, ... England Deaconess Hospital bring the total to 168 Of these 168 cases of combined diabetes and pernicious anemia, 93 were observed at the New England Deaconess Hospital To this number might be added certain patients presenting anemia and achlorhydria but in whom we have not yet been able to establish satisfactorily the diagnosis of pernicious anemia

Explanations of the increased frequency of this combination must take ...

anemia and diabetes, anemia was known to exist in the family, and diabetes was known to exist in 33 3 per cent of these families In 1500 consecutive cases of diabetes, pernicious anemia was present in a parent or sibling in 15 instances The accuracy of family histories for each disease errs on the side of understatement

Pathology.—The pathological changes in combined diabetes and pernicious anemia have been reported in nine autopsies

A tenth autopsy, Case 37754, was a single female aged fifty-one years, who entered the Deaconess Hospital on December 14, 1950, because of weakness, pruritus vulvæ, and paresthesiæ of the hands and feet Glyco-

[4] Combe Tr Med Chir Soc, *1*, 193, 1824
[5] Parkinson Lancet, *2*, 543, 1910
[6] Root Jour Am Med Assn, *96*, 928, 1931

Laboratory Features.—The precise diagnosis of pernicious anemia rests upon examination of the marrow which is characterized by numbers of megaloblasts when anemia is severe but may not be diagnostic in remission. In patients with neurological dysfunction, bone marrow examination may be crucial. The diagnosis of pernicious anemia was replaced by myeloma in the following patient with macrocytic anemia, achlorhydria, and ataxia. Case 10837, a male, aged forty-eight years, with diabetes for nineteen years, entered the New England Deaconess Hospital on October 14, 1951, complaining of a staggering gait, pain in the feet, and paresthesias of the hands. Coordination of the lower extremities was poor, the Romberg test was positive, and vibratory perception over the malleoli was decreased. Histamine achlorhydria was present. The red blood count was 3,700,000, the hemoglobin 11.5 grams per cent, the hematocrit 38 per cent. The spinal fluid protein was 29 mgs. per cent. Acid and alkaline phosphatase, serum bilirubin, and total plasma proteins were normal. No Bence-Jones protein was found in the urine. Bone marrow examination revealed marked [illegible]

The patient died in 1953.

Ehrenfeld[9] warns that in the presence of infection, the bone marrow in pernicious anemia may be non-megaloblastic. This should be considered particularly in diabetics who are notoriously prone to both acute and chronic [illegible]

In cases of pernicious anemia the anemia is macrocytic and normochromic. All 28 of the present cases had definite macrocytosis, as determined by inspection of the blood smear or by calculation of the mean corpuscular volume. For example, the mean corpuscular volumes in the last three cases of pernicious anemia discovered at this clinic (Cases 39657, 2213, 37217) were 106, 116 and 138 cubic microns, respectively.

On the other hand, we have noted several diabetics with macrocytic anemias, with or without achlorhydria, who obviously did not have pernicious anemia. Macrocytic anemia is often noted in conjunction with liver disease. Indeed, Wintrobe[11] found macrocytic anemia in 32.6 per cent of 132 cases of liver disease. Sturgis and Goldhamer[12] cited 10 cases of macrocytic anemia not due to pernicious anemia. Their cases with liver disease showed typical reticulocyte responses to liver extract, which also occurred in a diabetic with acute hepatitis and macrocytic anemia, as reported by Root.[13] The macrocytosis in these cases may be due to depletion of stores of the erythrocyte-maturation factor, although a deficient diet may play a role, particularly in alcoholic cirrhosis. Occasionally the anemia with liver disease may be truly megaloblastic. Movitt[14] reported 2 cases of

[illegible] 4, 86, 1950
Jour. Med. Sci., 223, 54, 1952

, 12, 1215, 1949
45, 1935

clinical findings are present, no difficulty arises in the recognition or diagnosis of the latter. However, because the symptoms and signs of pernicious anemia oftentimes develop in an insidious manner and have certain similarities to those of diabetes, the diagnosis may be seriously delayed

The diabetic skin frequently is lax, pale and cool, suggesting an anemia which is not found upon examination of the blood. In acidosis, on the other hand, the flushed cheeks serve to disguise true anemia. A yellowish tint of the skin due to carotinemia, which is common in diabetics, is easily differentiated from the lemon tint of pernicious anemia by its intensity upon the

mentary system in pernicious anemia Although constipation is more common in diabetic patients, they also suffer from diarrhea Frequently the diarrhea of diabetes is nocturnal and responds to liver extract therapy.

Neurological disturbances, particularly paresthesiae of the hands and feet are common in both diabetes and pernicious anemia. The paresthesia of diabetic neuropathy frequently has a burning quality and is much worse at night In differentiating the neurological symptoms of diabetes and pernicious anemia, Rundles* has stressed this thermal paresthesia of the former Another striking clinical difference is the presence of pain in diabetic neuropathy and its virtual absence in subacute combined sclerosis. Manifestations of autonomic nerve involvement occur much more frequently in diabetes The atonic bladder and nocturnal diarrhea are common examples of diabetic visceral neuropathy. The frequency of pyramidal

fluid protein is elevated in diabetic neuropathy. The changes in the central nervous system due to diabetes are usually temporary, responding to treatment, and relief can be promised. In pernicious anemia, however, the spinal cord lesions are difficult to improve. Table 91 lists some of the neurological similarities and differences between the two conditions.

TABLE 91 —DIABETIC NEUROPATHY VERSUS SUBACUTE COMBINED SCLEROSIS

Signs and Symptoms	*Diabetes Mellitus*	*Pernicious Anemia*
Paresthesiae	Common	Common
Decreased Vibratory Sensation	Common	Common
Areflexia	Common	Occasional
Autonomic Dysfunction	Common	Occasional
Hypesthesia	*Common*	Rare
Pain	Common	Rare
Hyperesthesia	Common	Rare
Paralysis	Common	Rare
Ataxia	Rare	Common
Incoordination	Rare	Common
Spasticity	Rare	Common
Hyper-Reflexia	Rare	Common
Babinski Response	Rare	Common
Mental Aberration	Rare	Frequent

* Rundles' Loc cit p 497

C HEMORRHAGIC DISEASES

Hemorrhage occurs in association with: (1) faulty coagulation of the blood; (2) defective numbers or function of blood platelets, or (3) vascular weakness. Thrombocytopenic purpura has occurred in only 3 diabetics at the New England Deaconess Hospital. A male, age 28, died from hemorrhages in the skin, meninges and intestine, causing intussusception. Splenectomy saved the other two. Aplastic anemia caused the death of Cases 27222, and 5327. Thrombocytopenic purpura as a probable manifestation of allergy to insulin occurring in a diabetic man, aged 60 years, with platelets 27,000, and blood sugar 309 mgs. is described by Constam.[22a] Cortisone was used after the emergency ended. In vitro tests for insulin as the allergen were positive.

D COAGULATION DEFECTS

Coagulation defects occurred in two notable cases, Case 46979, a girl age 7 years, who became rapidly unconscious, was treated for acidosis in another city, then came to the New England Deaconess Hospital with marked left-sided ataxia, and other signs pointing to a cerebellar lesion. At operation a large area of hemorrhage in the cerebellum was evacuated. Her blood, studied by Dr. James L. Tullis, showed a deficiency in SPCA, the specific protein conversion accelerator. Treatment of this congenital blood [illegible]

the uterus was stony hard. Four transfusions failed to stop vaginal bleeding and at the end of four hours she entered the Boston Lying-in Hospital [illegible]

pregnancy and was well in September, 1958.

E POLYCYTHEMIA

Polycythemia of primary type has occurred in only 8 diabetic patients in the Joslin Clinic experience. Dr. David C. White,[23] has summarized the records of 76 cases of well documented polycythemia vera and 18.4 per cent (14 cases) proved diabetic clinically or by glucose tolerance test. Twenty-six cases of combined diabetes and polycythemia were compared with 62 cases of uncomplicated polycythemia and 100 diabetics of similar age. Myocardial infarction, cerebro-vascular accidents, peripheral arterial insufficiency and other thrombotic accidents were three times as frequent in

[22a] Constam. Diabetes, 5, 121, 1956.
[23] White. In press.

cirrhosis of the liver with megaloblastic bone marrows and macrocytic anemias. Neither patient had achlorhydria, and only one responded to liver extract.

Histamine achlorhydria frequently is associated with diabetes mellitus, particularly in older patients. The usual estimation is that from 30 to 40 per cent of diabetics have anacidity. Consequently, the combination of anemia, achlorhydria, and neurological symptoms often occur in diabetics and clinically may mimic pernicious anemia in varying degrees.

The reticulocyte response in diabetic patients with pernicious anemia may be a diagnostic pitfall. The response following liver or vitamin B_{12} therapy should not be used as the sole diagnostic criterion for pernicious anemia. Frequently, in diabetic patients with pernicious anemia, one observes a rise of reticulocytes only to 5 or 6 per cent within four to five days after beginning treatment with liver extract or vitamin B_{12}, particularly if the anemia has been mild. This is in marked contrast to the usual rise of 20 to 25 per cent that occurs in non-diabetics. Case 2213, a woman, aged seventy-six years, who had had diabetes thirty years, exemplified how slight the reticulocyte response may be. On November 7, 1951, the diagnosis of pernicious anemia was established by examination of the bone marrow. The hemoglobin was 56 per cent Two months later the hemoglobin was 77 per cent although the greatest reticulocyte response was only 4 0 per cent. Only liver extract was used in treatment

Treatment.—Protein, adequate in amount and character, is essential in the dietary treatment Acidosis and coma, as well as partially controlled diabetes, particularly when infections are present, lead to faulty protein metabolism Three of the present 16 cases have had coma. In the present cases the usual diets at discharge from the hospital provided for 175 to 200 grams carbohydrate, 80 to 110 grams protein, and 80 to 120 grams fat Insulin prescribed in 13 cases varied from 6 to 70 units daily. All cases received liver extract or Vitamin B_{12} parenterally in dosages planned to produce a normal hemogram and neurological improvement. In our experience every case who has received adequate liver treatment and adequate diabetic treatment has shown no increase whatever in the symptoms due to central nervous system involvement

It appears since West's report[15] that Vitamin B_{12} is as effective as liver extract in controlling the hematological and neurological manifestations of pernicious anemia [16] In spite of the beneficial hematinic effect of folic acid (pteroylglutamic acid)[17] it appears now that the neurological abnormality may proceed unabated or recur [18 19 20] Folic acid has no adverse effect on normal individuals or individuals with anemias other than pernicious anemia [21 22]

15 West ... Science ..., 398, 1948

... 90, 1056, 1945

... , 1950

six minutes, clotting time was twelve minutes Van den Berg, 0 4 direct, 0 6 indirect Urobilinogen was 2 2 Erlich units per 2 hours, normal less than 1 Prothrombin time, 72 per cent, Prothrombin consumption, decrease, Bromosulphathalein, 2 per cent retention, stool guaiac, positive Patient had a positive platelet agglutinin test by Dr. James L Tullis Serum calcium, 9 0, Serum phosphorus 3 1 Following splenectomy, the platelet count rose to 490,000 The enlarged spleen showed many nodules consistent with sarcoid

Agranulocytic angina has occurred in seven of our diabetic patients All were females Case 17292, who had had diabetes for one year, died in December, 1938, of pneumonia and agranulocytosis She had received phenacetin for three days, the white blood count was as low as 700. Case 5672, a diabetic for fifteen years, received sulfadiazine during coma for axillary abscesses in September, 1943 The white blood count fell to 1,350, but she recovered with penicillin therapy She died in July, 1949 Case 30440, a diabetic for five years, entered the Deaconess Hospital because of a high fever The white blood count was 600 (all lymphocytes) She had received sulfadiazine during the treatment of a perinephric abscess two weeks before She died of E coli septicemia in May, 1947 Prior to the introduction of antibiotics, fatal agranulocytosis developed in 4 other women coincidentally with severe infections

G LEUKEMIA

Thirty-two cases of combined diabetes and leukemia have been observed at the New England Deaconess Hospital The twenty males and twelve females ranged in age from fifty to eighty years, with one exception In only 2 instances did the onset of leukemia definitely precede the onset of diabetes In 3 cases precedence could not be determined The types of leukemia and the number of each were as follows chronic lymphatic, 16, chronic myelogenous, 4, acute myelogenous, 4, acute lymphatic, 5, chronic monocytic, 1, aleukemic myelogenous, 1, and aleukemic lymphatic, 1 Retinitis proliferans occurred in 2 cases, and diabetic coma in one

H LYMPHOMA

Twenty-two cases of co-existing lymphoma and diabetes have been observed at this Clinic One-third of the cases were Hodgkin's disease Case 14122, was of particular interest, for terminally he displayed severe hypoglycemia without insulin Diabetes began in 1935, at the age of fifty-one years In March, 1951, a biopsy of an inguinal node disclosed a macrofollicular lymphoma When he entered the New England Deaconess Hospital in September, 1951, for x-ray therapy over the abdomen, he was taking 10 units of NPH insulin Insulin was stopped September 21, 1951, because of reactions The periods of hypoglycemia persisted in spite of frequent feedings of carbohydrate, and on October 4, the fasting blood sugar was 0 025 per cent Cortisone improved his condition only slightly, and he died October 7, 1951 At autopsy, the tumor was largely retroperi-

the patients with combined diabetes and polycythemia as in the diabetic control group Hemorrhage occurred chiefly when the erythremia became "burned out" and was associated with long duration of the polycythemia splenomegaly, myeloid metaplasia, thrombocytosis, leukemoid reactions anemia and terminal leukemia. Common manifestations of polycythemia appeared in the combined group, especially with complications including peptic ulcer, epistaxis, hypertension and gout. Common symptoms were pruritus, painful toes, paresthesiae, suffused conjunctiva and splenohepatomegaly.

The polycythemia usually began in the fifth or sixth decade and was a little more frequent in women than in men.

Although the diabetic component seemed mild, retinopathy, neuropathy and especially nephropathy were frequent when polycythemia complicated diabetes. A possible genetic relationship was suggested by a family history of diabetes in 10 per cent of the non-diabetic polycythemic patients

The sustained elevation of red cells and hemoglobin, often accompanied by leukocytosis and a great elevation in the platelet level, were striking features. *The highest red count in a patient at the New England Deaconess Hospital was 8,700,000, with white cells numbering 29,000.*

F. THE LEUKOPENIC STATE AND AGRANULOCYTOSIS

Leukopenia with the white blood cell count below 4,000 cells per cc. has *frequently occurred in our patients with cirrhosis, splenomegaly and various* infection [illegible] Case 31362 [illegible] was discovere[illegible] white blood co[illegible] morrhages, the platelet count was reduced to 40,000, and Dr. James L Tullis *demonstrated the presence of platelet anti-bodies in the serum.* At operation, the spleen, the entire stomach and a portion of the pancreas were removed as a life-saving measure by Dr Richard H Sweet Within a few days the platelet count rose to 400,000 He died in 1958, in hepatic coma Esophageal veins were tremendously dilated. Case 44032, age 62 years, seen in consultation with Dr B J Buck of Hartford, had had leukopenia. His serum also presented antiplatelet factors and a large spleen had been noted by *x*-ray Before splenectomy could be done, he died of a coronary occlusion Case 44781, housewife, age 46 years, with diabetes of three years' duration, entered the New England Deaconess Hospital with pain from subacute cholecystitis The liver was not enlarged, but the spleen tip was palpable, three finger breadths below the left costal margin, firm and tender Ecchymosis occurred over the abdomen and thigh Pedal pulses were palpable There were no neurological changes *Hemoglobin* 11.1, white count 7,700 with 50 neutrophils, 14 bands, 21 lymphos, 5 monos, 5 eos, which all showed a moderate number of spherocytes. Urinalysis was unremarkable. Platelet count was 20 to 30 000, MCV 88, MCH 29; MCHC 33, Cephalin flocculation was 2 plus 48 hours, thymol turbidity 2 1 units, thymol flocculation, negative An osmotic fragility test showed *no abnormality*, reticulocyte count was 2.2 per cent. Bleeding time was

Chapter 22

THE EYES AND DIABETES

Howard F Root, M D , Jørn Ditzel, M.D , and Stanley Mirsky, M D

The conservation of vision has become the major objective in the treatment of severe diabetes It is true that frequently the first evidence of diabetes is manifested in the retina long before albuminuria or other warnings are found The prevention of deaths from coma and the control of the devastating infections are nearing accomplishment Today, the prevention or postponement of the lesions in the retina and the kidney are objectives which even with our limited and incomplete knowledge of their etiology seem possible of achievement The severity of diabetes has been measured in many ways but today severity appears to many students as best indicated by the presence of vascular, renal and retinal lesions as diabetic sequelæ For many years the relationship between diabetic retinitis and diabetic nephropathy with its Kimmelstiel-Wilson lesion was obscured by explanation of the diabetic retinal lesions on the basis of hypertension or arteriosclerosis As early as 1877 MacKenzie[1] presented in clinical form and with complete post-mortem pathologic data, a beautiful picture of the capillary aneurysms, retinal and vitreous hemorrhage, which are now recognized as characteristic of diabetic retinopathy Leber[2] had also described the retinal lesions Attention was first directed to the venous stasis, tortuosity and dilatation of retinal veins by Nettleship[3] Waite and Beetham[4] emphasized the lack of evidence for arteriosclerosis as the cause of retinal lesions Ballantyne and Loewenstein[5] rediscovered the retinal micro-aneurysms Today, the outstanding ocular danger is the specific diabetic retinopathy characterized by morphologic changes in the venules and capillaries with subsequent neovascularization These changes developing in young diabetic patients seem directly due to some disturbance which is a result of diabetes or associated with it The disturbance is probably in the functional relationship between insulin, other hormones and enzyme systems This may explain why the most skillful use of insulin, a good diet, good hygiene and medical supervision persistently followed postpone, or prevent such diabetic complications in most patients It may be expected that intensive research in this field where the influence of insulin and other hormones and enzymes upon metabolism is being investigated, will yield discoveries of practical importance in the preventive treatment of these complications

[1] MacKenzie Roy d London Ophthalmic Hosp Report, 9, part 2, p 152, 1877
[2] Leber Arch f Ophthal 21 238, 1875
[3] Nettleship Trans Ophthal Soc United Kingdom, 8, 159, 1888
[4] Waite and Beetham New England Jour Med, 212, 367 429, 1935
[5] Ballantyne and Loewenstein Trans Ophthal Soc United Kingdom, 63, 95, 1943

toneal, and the pancreas was completely destroyed. The adrenal glands and the liver were essentially normal except for inconsequential, microscopic foci of tumor cells The pituitary gland showed moderate atrophy and fibrosis. The cerebral cortical neurones showed hypoglycemic necrosis One patient with hypersplenism and pancytopenia from Hodgkin's disease underwent splenectomy with good result in September 1957.

I. FIBROCONGESTIVE SPLENOMEGALY (BANTI'S DISEASE)

Case 24159, a male, aged twenty-three years, entered the New England Deaconess Hospital on December 4, 1946, complaining of weakness and edema. Diabetes began in 1944. The spleen and liver were greatly enlarged, and there was marked edema and ascites Esophageal varices were demonstrated by *x*-ray The hemoglobin was 5 3 grams per cent and the white blood count was 8,700. Splenectomy, left nephrectomy and a splenorenal anastomosis were performed by Dr Richard H. Sweet. The pressure in a coronary vein at the lesser curvature of the stomach was 390 mm of water. The pathological diagnosis of the spleen was fibrocongestive splenomegaly. On March 3, 1950, because of recurring symptoms, a portocaval anastomosis was performed by utilizing a hugely dilated branch of the thrombosed portal vein. A liver biopsy disclosed subacute hepatitis He died of hepatic failure in 1956

Six other cases have had the clinical picture resembling Banti's disease, although final proof, either at autopsy or operation, is lacking

Diabetes and splenomegaly, with or without hepatomegaly, and without anemia, leukopenia or gastro-intestinal hemorrhage, were found in 35 cases between 1946 and 1956

Pennock and Lieder[24] reported a soldier, aged twenty-one years, with diabetes and Banti's disease. Following splenectomy the insulin requirement decreased Approximately six weeks after surgery, he developed infectious mononucleosis

[24] Pennock and Lieder Amer Jour Digest Dis *14*, 135, 1947

a level approaching systolic blood pressure, and consequent glaucoma of the hemorrhagic type This proliferative phase is pathognomonic of the severe diabetes of early life, while simple retinitis occurs frequently in the mild diabetes of later life.

(d) *Incidence.*—The present series has grown rapidly in recent years In Table 92 are summarized data on 847 cases recognized up to November 1,

TABLE 92 —RETINITIS PROLIFERANS IN 847 DIABETICS

	Age at Onset of Each Condition				
	0–19	*20–39*	*40–59*	*60 and Over*	*Total*
Diabetes					
Male	182	107	87	3	379
Female	169	113	177	9	468
Retinitis Proliferans					
Male	5	187	147	40	379
Female	9	171	188	100	468

1957 This number undoubtedly errs by understatement An equal number may be assumed to exist, although not as yet diagnosed In our re-examination of more than 400 patients under 45 years of age, with duration of diabetes of 10 to 25 years, for every patient with retinitis proliferans, approximately 5 were found with simple retinitis which had not yet reached the proliferative stage.

The series includes 379 males and 468 females, a sex distribution not far different from the distribution of diabetes in general Three hundred and fifty-one, nearly 42 per cent of the entire series, developed diabetes before the age of 20 years, in contrast to the fact that only 10 per cent of all diabetics had their onset in the first decades of life Diabetes began before the age of 40 years in 68 per cent of the series, whereas in only 12 cases did diabetes beginning after the age of 60 years lead to retinitis proliferans Only 14 cases developed retinitis proliferans in the period before the twentieth year

Long duration of diabetes and inadequate control of the condition were striking features in the great majority of patients Thus, in those patients whose diabetes began before the twentieth year, the average duration of diabetes before the discovery of the onset of retinitis proliferans was 17 1 years and no patients in this group developed the condition in less than 8 years For patients with diabetes beginning between the 20th and 40th year, the average duration of diabetes was 18 7 years In 6 patients diabetes had been known for only from 3 to 6 years and these patients were all between 35 and 39 years of age when the discovery was made In patients

frequent Diabetes without symptoms may have been present for years before its discovery

(e) *Clinical Course* —In the vast majority of cases, long duration of im-

Incidence of Blindness.—Although information as to the number of diabetic patients with impaired vision or blindness has at best been incomplete, recent estimates all show a substantial increase in blindness due to diabetes.[6] In the United States,[7] among 20,591 recipients of aid to the blind, in twenty states, 1.5 per cent were diabetic. The State of Massachusetts reported the highest rate for diabetic blindness with an incidence of 3.8 per cent. However, in the same state for the year ending December 1, 1957, 18 per cent of new persons on the register were diabetic. Similar changes are shown by other states. In England the report by Sorsby[8] showed an increase from 8.4 per cent of blindness due to diabetes in the period 1949 to 1950, to 13.3 per cent for the period 1951 to 1954, for the age group from 50 to 69 years.

Retinitis Proliferans.—Although any type of retinopathy seen in nondiabetics, may occur also in the diabetic, three types of lesion make up the vast majority of the changes developing in diabetic patients. All three are seen much more frequently since the discovery of insulin chiefly because of the prolonged duration of life made possible by the use of insulin and other aids in treatment. Proliferative retinopathy means severe diabetes.

(a) *Simple Diabetic Retinitis.*—Minute red dots seen with the ophthalmoscope in the fundus, are usually micro-aneurysms. They occur in other diseases, but much less frequently than in diabetes. Round hemorrhages, hard, and waxy exudates and small flame-shaped hemorrhages are frequently found. They may appear in young patients a few years after diabetes begins, but occasionally in older patients they are seen even before blood and urine tests indicate diabetes, or may occur in mild border-line diabetics.

(b) *Renal Exudates.*—Cotton-wool exudates, areas of edema and striate hemorrhages suggest a renal complication such as glomerulonephritis or development of the diabetic nephropathy.

(c) *Retinitis Proliferans.*—Progression from simple to proliferative retinopathy is almost pathognomonic of severe diabetes. In many patients the diagnosis is not made until sudden loss of vision from a hemorrhage into the vitreous, or into the retina, brings the patient to medical examination. By that time advanced changes may exist. The diagnosis of retinitis proliferans may be difficult in early stages. A striking feature is dilatation of venules. Where the veins are widened compression by slender arteries may give the appearance of a string of sausages. Venous anastomoses occur. Strands of dense, white, fibrous tissue may occur anywhere in the fundus, but more frequently at the disc. This membranous tissue may extend into vitreous. The most characteristic lesion is the formation of new blood vessels anywhere in the retina. The contraction of scar tissue may cause separation of the retina. Spontaneous hemorrhages often occur at night. A protein-rich transudate may be poured out from the capillaries with a resulting rise in ocular pressure from a normal level of twenty to

[6] Kerby: Nat. Soc. for ... o the
[7] Hurlin, Saffian and Ri...
Blind, Federal Security Age...
[8] Sorsby: Brit. Jour. Ph...

Exceptional patients have gone on from 5 to 7 years after some degree of nitrogen retention had been established. The duration of retinitis proliferans after its recognition is recorded in Table 93. It will be seen that in 75 patients, duration was less than two years. In 142 patients between two and five years, in 92 patients from 5 to 10 years, in 34 patients from 10 to 15 years and a total of 16 patients survived 15 years or more, 9 of whom were still living.

TABLE 93.—DURATION OF LIFE AFTER DIAGNOSIS OF RETINITIS PROLIFERANS
847 Cases

Years	*Living*	*Fatal*	*Total*
0–1.9	207	75	282
2–4.9	144	142	286
5–9.9	112	92	204
10–14.9	35	24	59
15+	9	7	16
	507	340	847

Formerly, the retinopathy advanced during pregnancy and constituted an indication for terminating pregnancy. However, in recent years actual improvement has been reported in the ocular lesions by Dr. William P. Beetham after pregnancy so that now, no pregnancies are terminated for this reason. Since all the pregnant girls received estrogen and progesterone, a trial is being made in the use of progesterone in other patients with retinitis proliferans.

Infections of the feet and gangrene have been rare in this group, requiring amputation in but a small number of aged patients. The *frequent association* of neuropathy has justified the use of the term "Triopathy." (See page 490)

Blindness occurred in 98 patients. Glaucoma is recorded in 78 cases and in 25 cases hemorrhagic glaucoma required removal of an eye.

(f) *Prognosis.* The causes of death in 331 cases of retinitis proliferans are shown in Table 94. The diabetic nephropathy with terminal uremia caused the death of 147 patients. Coronary occlusion was a terminal event in 98 patients. Cerebral accidents occurring in 20 patients, arteriosclerosis

perfectly controlled diabetes precedes the development of retinitis proliferans. The following exceptional case raises questions as yet unanswered

Case 49219, female, developed glycosuria at 19 years of age during her

tests until January, 1957, when polyuria and weight loss occurred In April, 1957, she was seen at the New England Deaconess Hospital for the first time. Blood sugar 234 mg per cent and glycosuria 2 6 per cent, albuminuria 60 mg. per 100 cc Serum cholesterol 248 mg per 100 cc Eye grounds were normal She used insulin and a weighed diet, remained sugar free until October, 1957, when she suffered a vitreous hemorrhage. On January 6, 1958, Dr William P. Beetham made the following report:

> "In the right fundus there are a few new vessels on the optic disc. There are at least 6 or 7 small areas of *neovascularization at the* retinal level seen in various portions of the fundus. There are some nests of micro-aneurysms and scattered punctate hemorrhages in moderate number There is a festoon of new tissue nasal to the
> The veins
> 3); the
> In the
> There
> are micro-aneurysms and punctate hemorrhages scattered in various portions of the retina. There is a little new tissue present in the nasal fundus. There are several areas of new capillary formation *all at the retinal level* "

pillary
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youngest, in a series of 100 cases who had developed retinitis proliferans in a short period of time, was 35 years of age with diabetes of 6 years duration

Usually it is patients under 30 years of age whose use of insulin has been delayed or inadequate and whose diet has been improper with resulting
glycosuria, who most frequently

Within months or years albuminuria develops Frequently edema of the ankles has occurred before albuminuria appears and perhaps a stage of nephrosis has become manifest In this period of nephrosis albuminuria may be massive, blood cholesterol
This

period renal function declines and nitrgoen retention begins. In this series of 847 patients most of the older ones have come for treatment of diabetes only after lesions are far advanced. The length of time between the early stages and terminal phase may vary widely

development of the proliferative phase in nearly all cases Time intervals between the appearance of the first retinal hemorrhages and the development of the proliferativ
progression from early
2 or more years in an
abnormal capillary fragility and permeability has been attempted by many students making use of flavonoids and ascorbic[9a] acid. Hesperidin, CVP, and Rutin among other substances have been given thorough trial with varying reports Although, in our youthful patients the use of Rutin in doses of 300 mg to a 1000 mg per day has reduced the capillary fragility

insulin requirements reduced, further study and more data will be required before judgment as to any genuine, persisting benefits may thus be secured In our two young patients undergoing hypophysectomy, because of advancing retinopathy and before albuminuria had occurred, no definite resorption of hemorrhages has been seen A third patient, operated elsewhere, died shortly post-operation Certainly, if benefit is to be anticipated
pophysis, operation should be

inges in the retina usually are
sequelæ and can be observed
directly with the ophthalmoscope, the diabetic retinopathy has become the

level is not possible and it has proved most difficult to translate the descriptive terminology derived from ophthalmoscopic studies into terms of basic pathology The histologic picture is characterized by the following retinal lesions (*a*) microaneurysms, (*b*) phlebopathy, (*c*) proliferating new-formed vessels, (*d*) hemorrhages, (*e*) exudates

(a) *Microaneurysms* — The admirable study by Ballantyne[11] in 1943 clearly disclosed that most of the so-called punctate hemorrhages observed ophthalmoscopically were actually microaneurysms There was some controversy at first as to whether they were primarily arterial or venous in origin The general concensus now strongly favours the latter source particularly capillaries and small venules They have also been described in

Booth
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by the patient are of primary importance. *Although it must be admitted* that occasional cases of retinitis proliferans develop in patients soon after the discovery of diabetes, and in whom no acidosis, no infection, and no albuminuria had been present, nevertheless, the vast majority of the patients in our series have had long periods of relatively uncontrolled diabetes.

TABLE 94.—CAUSES OF DEATH IN 331 CASES OF RETINITIS PROLIFERANS

	Age at Death (in years)				
	0–19	*20–39*	*40–59*	*60+*	*Total*
Nephropathy		86	39	22	147
Coronary		28	24	46	98
Cerebral Accident		2	6	12	20
Arteriosclerosis		4	5	17	26
Gangrene		1	1	5	7
Coma		1	1	1	3
Hypoglycemia		1			1
Misc (Pulm TB, Cancer, *etc*)		8	8	13	29
	0	131	84	116	331

The severity of diabetes depends more on the age at onset than on any other *single factor, although long duration is also of major importance.* Measurements of severity dependent on insulin dosage are notably unreliable. Many temporary factors including improper diet, lack of physical exercise, infections, allergy, and renal status will modify greatly the insulin requirement. Variations in dosage among our patients during their hospital stay. (See *Table 95*) illustrate the declining insulin dose with advancing renal failure and with increasing care in observing dietary rules, since many of the 249 cases [illegible] required much higher dosage [illegible] s daily were patients with [illegible] year.

TABLE 95.—INSULIN DOSAGE 847 CASES RETINITIS PROLIFERANS

Units	*Cases*
0	22
0–10	53
10–25	174
25–60	473
60–120	124
180	1

In order to use insulin *dosage as a measure of severity, one would need* periods of observation, with daily measured diet and exercise, sufficiently long to include the marked variations in the diabetes itself, often without evident cause The severity of diabetes with onset early in life depends

development of the proliferative phase in nearly all cases Time intervals between the appearance of the first retinal hemorrhages and the development of the proliferative changes must vary greatly Beetham[9] recorded ... retinopathy in

and Rutin among other substances have been given thorough trial with varying reports. Although, in our youthful patients the use of Rutin in doses of 300 mg to a 1000 mg. per day has reduced the capillary fragility in some cases, the effects have seemed to bear no relation to the course of the disease, especially after the proliferative phase has become apparent.

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insulin requirements reduced, further study and more data will be required before judgment as to any genuine, persisting benefits may thus be secured In our two young patients undergoing hypophysectomy, because of advancing retinopathy and before albuminuria had occurred, no definite resorption of hemorrhages has been seen A third patient, operated else-

the first decisive signs of the late-diabetic sequelæ and can be observed directly with the ophthalmoscope, the diabetic retinopathy has become the natural cornerstone in the study of vascular disease in diabetes However, a serious limitation of ophthalmoscopy is the fact that even with the most modern instruments, a direct study of the retinal blood vessels at a cellular level is not possible and it has proved most difficult to translate the descriptive terminology derived from ophthalmoscopic studies into terms of basic pathology The histologic picture is characterized by the following retinal lesions (a) microaneurysms, (b) phlebopathy, (c) proliferating new-formed vessels, (d) hemorrhages, (e) exudates

(a) *Microaneurysms.*—The admirable study by Ballantyne[11] in 1943 clearly disclosed that most of the so-called punctate hemorrhages observed ophthalmoscopically were actually microaneurysms There was some controversy at first as to whether they were primarily arterial or venous in origin The general concensus now strongly favours the latter source particularly capillaries and small venules They have also been described in

... To be published
... urg., 12, 535, 1954
... Barnes Am Jour
... Jour., 2, 72, 1955

detail by Friedenwald[12] and Ashton[13] as globular or saccular in shape and varying from 30–90 microns in diameter. In diabetes, with few exceptions, the microaneurysms are situated in the inner nuclear layer, in the venous side of the small blood vessels, which link the deeper and superficial plexus of the retina. Friedenwald and Ashton likewise found that the majority of hemorrhages, either by diapedesis or by rhexis, arose from the aneurysms. Clusters of exudates commonly surrounded the aneurysms suggesting that they were formed by leakage of plasma through the aneurysmal wall. Lundback[14] found a fairly good relationship between the number of ophthalmoscopic visible sanguinolent dots and the number of microaneurysms subsequently found in the venous part of the capillaries and in the smaller venules of the histologic observations. It is these observations which make it so necessary to elucidate the mechanism leading to the microaneurysms.

By using Sudan and Scarlet R staining, Ballantyne[15] furthered his in- [illegible]

histologic characteristics of hyaline and sometimes these thickened walls show concentric lamellæ as if successive layers of the material had been laid down. Friedenwald[16] applied the Hotchkiss-MacManus Technique *(PAS stain) to the whole flat retina preparation and found that the basement membranes became stained an intense red.* The stain was more concentrated in the walls of the aneurysms and from this Friedenwald suggested an abnormality in the mucopolysaccharide metabolism in relation to diabetes and diabetic retinopathy. Ashton[17] and later Friedenwald[18] both drew attention to the similarities between the staining characteristics of the retinal and kidney glomerular hyalin. Ashton believed that intercapillary glomerulosclerosis and retinopathy were manifestations of the same pathologic process modified by the different anatomical structure of the retinal and glomerular vessels. Other than in the retina microaneurysms were not found either in the eye, in the cerebral vessels, or in the vessels of serous membranes, bladder or omentum. Their confinement to the retina, according to Ashton, is related to venous stasis and the peculiar structure of the retinal capillary network in the inner nuclear layer. The stages in the development of microaneurysms from the normal capillary is not known. Besides the globular microaneurysms other ectasiæ may occur on the retinal capillaries. Sometimes, relatively long segments of the capillaries are so

[12] Friedenwald. Am. Jour. Ophthal., *32*, 487, 1949; Soc. Trans., Arch. Ophthal., *60*, 124, 1953.
[13] Ashton. Brit. Jour. Ophthal., *33*, 407, 1949.
[14] Lundbaek. Long-term Diabetes, London and New York, Lange and Maxwell, 1953.
[15] *Ballantyne.* Arch. Ophthal., *33*, 97, 1945.
[16] Friedenwald. Loc. cit., p. 548.
[17] Ashton. Loc. cit., p. 548.
[18] Friedenwald. Loc. cit., p. 548.

dilated as to form sausage shaped loops or they may form complex coils Ashton depicted the development of microaneurysms as beginning either

rysms actually represented aborted attempts of neovascularization

From a morphologic point of view the retinal microaneurysms are not specific for diabetes However, in the cases in which a relatively large number of microaneurysms have been demonstrated, they have been confined to conditions associated with prolonged venous stasis in the retinal circulation Ballantyne[20, 21] Loewenstein and Garrow,[22] Becker and Post,[23] and Ashton[24] have all reported on the presence of numerous microaneurysms in cases of central retinal vein thrombosis The occurrence of retinal microaneurysms has also been demonstrated in Eales disease (periphlebitis

ing and injection techniques In this group in which no eye disease was suspected and in which no gross ophthalmological findings were to be expected in life, retinal microaneurysms were found in 29 per cent of the cases However, in about half, the lesions were confined to the extreme periphery of the retina, they were small and few in number, but occasionally indistinguishable from the diabetic type of aneurysm Ashton concluded, that apart from vascular sclerosis the occasional microaneurysm is the most common pathological lesion in the retina Diabetes stands out as being the disease in which microaneurysms are seen most frequently, in greatest

factors Ashton suggested that suboxydation and subnutrition of the vessel walls could be the underlying mechanism brought about either by a failure of the blood supply or by stasis of the venous circulation as in venous thrombosis and probably in diabetes

(b) *Phlebopathy* —Even though von Michel,[28] Nettleship[29] and Hirschberg[30] in the last century mentioned the venous retinal changes, it is only in the last two decades and coincidental to the increased longevity of young

configurative irregularities As mentioned some investigators consider this

[19] Wise Trans Am Ophthal Soc , 54, 1, 1956
[20] Ballantyne and Loewenstein Brit Jour Ophthal , 28, 593, 1944
[21] Ballantyne Trans Ophthal Soc United Kingdom, 63, 137, 1943
[22] Loewenstein and Garrow Am Jour Ophthal , 28, 840, 1945
[23] Becker and Post Ibid , 34, 677, 1951
[24] Ashton Loc cit p 412
[25] Wexler and Branower Arch Ophthal , 44, 539, 1950
[26] Wise Loc cit p 549
Ashton Loc cit p 549
[28] von Michel Deutsch Arch f klin , Med , 22, 439, 1878
[29] Nettleship loc cit , p 541
[30] Hirschberg Ztschr f prakt Augen , 21, 206, 1897

venous feature to precede the formation of microaneurysms.[31,32] Many ophthalmologists, however, do not regard the venous change an "abnormality" before more marked alterations, such as localized bulks, sausage-shaped dilatations and "bead-string veins" are present.[33,34] The presence of severe varicose venous changes in the retina of young individuals is almost pathognomonic of diabetes. According to Lundback[35] the phlebopathy is predominantly a phenomenon of young long-term diabetics Agatston[36] and Jensen[37] commented upon the prognostic importance of the ophthalmoscopical condition of the retinal veins. In their experience the combination of "sanguinolent dots" and exudates in the presence of normal retinal veins indicated good prognosis. Engorged retinal veins indicated an impending tendency
or vitreous chamber.
without secondary gl
the observation of retinal vein thrombosis in young diabetics is not uncommon [38] The cause of the caliber changes in the veins appears to be due to an abnormal vasomotor response related to the diabetic condition. (See page 552.)

(c) *Proliferating New-Formed Vessels.*—Nettleship[39] was the first to describe the presence of proliferative new-formed vessels in a patient with diabetes. However, Klien[40] and Hanum[41] were the first who gave detailed descriptions of proliferating retinopathy. Ashton showed that the new-formed vessels could arise from the microaneurysms or from small venules In a later work Ashton[42] showed that in severe cases of retinopathy in which

enumerated the various conditions in which such proliferation took place, *i e*, diabetes, retinal vein occlusion, Eales disease, sickle cell anemia, malaria, *etc* and classified the condition. The nature of the stimuli which excite and direct the growth of blood vessels into the retina in both normal and abnormal circumstances is as yet unknown However, it may be appropriate to mention some observations related to the experimental production of retrolental fibroplasia which indicate that some factor related to hypoxia in the retinal tissue is pre-eminently determining the new-vessel growth In a masterful presentation Michaelson[44] showed that the forma-

[31] Agatston Arch Ophthal, 24, 252, 1940

Il, Charles C

tion of retinal capillaries is solely a function of the retinal veins and that if a vein and an artery are close to each other a growth takes place predominently from the side of the vein remote from the neighboring artery He pointed out the capillary-free zone around the arteries both in the immature and mature retina. These anatomic facts suggested to Michaelson the presence in the retina of a vasoformative factor possibly biochemical in nature which was present in gradients of concentration differing in arterial and venous neighborhoods To Campbell[45] the only adequate explanation of all the observed features of vessel growth in the normal retina was that this vasoformative factor was related to low oxygen tension Campbell tested this hypothesis by placing one-day old rats in a low oxygen tension and made the significant observation that the capillary-free zone around the arteries became considerably narrower than in the control animals Ashton,[46] when investigating the effect of hyperoxia on the retina of the kitten found the converse, that raised oxygen tensions lead to widening of the capillary-free zone Even though these experiments were made on new-born animals and corresponded to clinical observations in retrolental fibroplasia in man, the capacity of veins and capillaries to form new vessels does not disappear at birth but lies dormant in the mature retina According to Ashton[47] new-vessel formation can be stimulated when three basic requirements are present (1) the presence of living cells to insure an active metabolism, (2) a low oxygen tension to promote anaerobic metabolism, and (3) a poor venous drainage to permit the accumulation of anaerobic metabolites wherein the vasoformative factor probably lies It should be recalled that the retina has the highest rate of respiration of any tissue and a higher rate of glycolysis in air than most other tissues[48] It was also suggested by Warburg[49] *et al*, that the various layers of the retina possess their own peculiar metabolism, some of the cells being responsible for the

letely oxidative
ported by other
diabetes patho-
Ashton[52] have
always been associated with underlying areas of obliterated capillaries or obstructed veins in the retina Here it may be suggested that the vasoformative factor is elaborated in the hypoxic retinal tissue and failing to drain away seeps into the vitreous where it reaches a concentration sufficient to stimulate the vessels to grow inward. Ashton also believed this concept of a preformed factor diffusing through the vitreous was applicable to the problem of neovascularization of the iris which is not an uncommon phenomenon associated with severe diabetic retinopathy

(d) *Hemorrhages* Beside the "punctate hemorrhages" and microaneurysms from which alone the presence of diabetes can be inferred, larger

Campbell Trans Ophthal Soc United Kingdom, *71*, 287, 1951
Ashton Ward and Serpell Brit Jour Ophthal, *38*, 397, 1954
Ashton Am Jour Ophthal, *44*, 7, 1957
Warburg Biochem Ztschr, *184*, 484, 1927
Warburg *et al* Ibid, *152*, 309, 1924
Sjostrand Jour Cell Comp Physiol, *42* 45, 1953
Strominger and Lowry Jour Biol Chem, *213*, 635, 1955
Ashton Loc cit, p 551

hemorrhages of various shapes can occur They are not typical and may take place in any region of the fundus Occasionally pre-retinal hemorrhages may rupture into the vitreous body.

(e) *Exudates* —In addition to the hemorrhages, numerous small exudates are found They are in the beginning small and discreet, either white or with a yellowish tinge. Later, they have a tendency to coalesce. Occasionally, they may aggregate and form circinate figures [63] Histologically they consist of hyaline material mixed with lipid and are usually situated in the deeper layers of the retina surrounding the microaneurysms [64] Ashton found that the hyalin exudates stained red with PAS stain showed an affinity for silver stain which occasionally demonstrated a laminated structure.

[illegible]

scope makes impossible the study of the retinal vessels at a cellular level *The only place in which detailed observations of the smaller blood vessels* can be made *in vivo* is in the bulbar conjunctiva. At the New England Deaconess Hosptial we have conducted an extensive investigation of the conjunctival blood vessels in living, young diabetics with the supposition that the functional disease, diabetes, might reflect functional changes in the smaller blood vessels which ultimately would lead to degenerative lesions Ditzel,[65] by using the stereo-binocular microscope, compared the conjunctival vessels in 220 diabetic and 175 non-diabetic individuals of various age-groups between 4 and 75 years of age. He found that the significant vascular changes in the diabetics consisted of irreversible, degenerative changes which were markedly accelerated as compared with normal aging, along with reversible vasomotor changes The reversible response changes consisted of various degrees of venular dilatation (loss of tone) and arteriolar constriction, which formed a set of pathologic vasomotor responses designated Vascular Pattern I and II The direct effect of these vasomotor [illegible] is a marked decrease rate of blood [illegible] blood to the venules and periodic [illegible] In diabetic children the irreversible degenerative changes in the vascular bed could be correlated with increased duration of diabetes [66] The presence of abnormal vasomotor patterns be-[illegible] When the conjunctival [illegible] day, [illegible] stion [illegible] with [illegible] nges- [illegible] aries

[63] Houston and Wise Arch Ophthal, *58*, 777, 1957
[64] Friedenwald Loc cit, p 185
[65] Ditzel Loc cit, p 180
[66] Ditzel and Duckers Loc cit, p 413
[67] Ditzel and Camerini-Dávalos Loc cit, p 414

and venules would increase and exudation discontinue In the cases in which such changes were encountered the venular congestion was least marked in the later afternoon at the time when dietary intake and insulin effect might be expected to produce the optimal daily metabolic pattern. Pregnancy and infection aggravated the degree of vascular response Ditzel

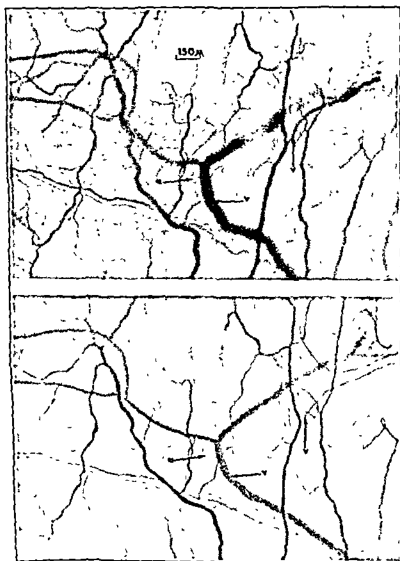


FIG. 26 Reversibility of venular congestion occurring over the period from 8 A.M. (*top*) to 5 P.M. (*bottom*) of the same day (see text). *a* arteriole, *v*, venule

and Moinat[58] studied the responses of the smaller blood vessels and the serum proteins during pregnancy in 30 diabetic compared with 30 non-diabetic individuals. In the pregnant diabetics the changes in the vascular bed and in the serum proteins (particularly the lipoproteins and glycoproteins) showed marked fluctuations in contrast to the normal pregnancy cases. The degree of vasomotor changes was favourably influenced by optimal dietary and insulin prescriptions. In order to evaluate whether these vasomotor responses were related to the development of retinopathy and nephropathy, a study of the vascular response patterns observed microscopically in the bulbar conjunctiva was made in 60 young diabetics with varying degree of complications.[59] A significant relationship between the degree of small blood vessel degeneration and the conjunctival pattern abnormality was found. Because the duration of diabetes and the various degrees of immediate metabolic adjustment were comparable in the groups, it strongly suggests that the reversible vasomotor changes play an important role in the development of diabetic retinopathy. The ophthalmoscopic retinal findings are not strictly comparable to those of the bulbar conjunctiva. The ophthalmoscope cannot disclose caliber changes in the terminal arterioles and smaller venules, but does demonstrate the disturbance of the arteriolar-venous ratio of the young diabetics. Venous dilatation and engorgement in the retina is a common finding and occurs not only in the cases of retinopathy but also in cases prior to this. So characteristic even though not specific is the finding of distended veins alone, that some investigators regard this as the initial sign of retinopathy. It is likely that the long term presence of the abnormal vasomotor response, venular dilatation, with the associated stasis and exudation leads to morphologic changes in the endothelium and basement membranes of the retinal capillaries and venules and that the microaneurysms and neovascularization are produced in response to the relative retinal anoxia.

In recent years evidence that the metabolic disturbances consequent upon insulin deficiency constitute a major factor in the production of the vascular, renal and retinal lesions of diabetes, is afforded in the reports of retinopathy in the diabetes of hemochromatosis,[59a] retinopathy and classical diabetic glomerulosclerosis with both nodular and diffuse lesions[59b] in gross pancreatic fibrosis and of retinopathy in the diabetes following pancreatectomy[59c] and relapsing pancreatitis.[59d]

In the five cases of hemochromatosis, Dr Hudson described conjunctival microaneurysms in 4 who were either truly diabetic or who had an abnormal glucose tolerance curve. In one diabetic, Case 2, retinal microaneurysms plus small patches of retinal hemorrhage were seen. The case reported by Duncan *et al*, male, age 48, had severe diabetes for 30 years, which had developed at the age of 19 years. Hypoglycemic episodes were frequent, even though his insulin dose was only 28–40 units. Diabetic retinopathy

consisting of microaneurysms, round-blob hemorrhages and discrete exudates plus varicosities of retinal veins, had been observed as well as proteinuria. Autopsy showed a pancreas consisting mainly of fibrous tissue and nodules of calcium with a little identifiable pancreatic tissue. The kidneys showed both the classical nodular and the diffuse hyaline sclerosis

that this case gave strong evidence in favor of the view that the retinal and renal complications were consequences of the metabolic disorder resulting from insulin deficiency.

In the case of Burton, a patient developed diabetic retinopathy three years after the onset of diabetes, which followed total pancreatectomy for adenoma of the islets. On a visit 7 years later, retinal hemorrhages had increased.

Sprague described a patient who developed relapsing pancreatitis at the age of 27 years and became diabetic 8 years later. After a further 9 years he was found to have a specific diabetic retinopathy.

Finally, Dunlop[58a] records, in a personal communication, the presence of specific retinopathy in a patient with diabetes of long duration resulting from hemochromatosis.

Prevention of Retinopathy.—Despite a general feeling that the control

degree of uncontrolled diabetes, was shown in 1934[60] to be followed within three years by the development of active pulmonary tuberculosis in 1 case out of 12 at the New England Deaconess Hospital. Indeed, 22 per cent of the deaths in patients in the years following recovery from diabetic coma were due to pulmonary tuberculosis.

White and Waskow[61] showed that after twenty years of diabetes childhood cases who had incapacitating vascular and retinal lesions coma had occurred in 75 per cent of t
began between the ages of fif
found the development of
glomerulosclerosis to be much more frequent with patients under poor control than und
Sherrill[62] and by

The later repor
whose diabetes had begun at ages varying from infancy to twenty-nine
years. None had had diabetes for less than ten years. This ...

selected group except that the patients were all alive at periods varying from ten to thirty-four years after the onset of diabetes. Careful study was made by *x*-ray examination of the arteries of the legs and pelvis, ophthalmoscopic examination by certified ophthalmologists and intensive blood studies. Among 247 patients a group of 37 patients under excellent and good control had developed neither marked retinal changes nor diabetic nephropathy over periods from ten to thirty-four years in duration. In 134 of the 247 patients no hemorrhages or exudates were to be found in the retina. In 103 patients whose diabetes had lasted from twenty to thirty-four years 3 of the 4 cases with excellent control had no retinal lesions whatever. Of the 54 cases with moderate to marked retinopathy all but 5 had had poor or only fair control, none had had excellent control No case

TABLE 96 —AGES OF DIABETIC AND CONTROL GROUPS

Age	Diabetics No	Diabetics Per Cent	Non-diabetics No	Non-diabetics Per Cent
Under 20	297	15		
20-39	302	15	75	16
40-59	776	39	269	59
60-up	627	31	113	25
	2002		457	

With the aid of Dr Nils Keiding[66] this series has been increased to 451 cases Among 179 patients similarly examined during 1951, 41 patients had absolutely normal eye grounds. No patient with excellent or good control showed advanced arterial calcification or retinitis even after periods of twenty to thirty-four years of diabetes Whatever the specific etiologic factors causing diabetic degenerative lesions may be, (endocrine, infectious, or metabolic), this series has demonstrated that the regulation of diabetes controls these factors The control of diabetes thus appears more important than any other known factor such as duration or severity of diabetes in preventing or ... in the retina

Other Ocula ... o quote freely and to extract ... tham[67] They examined, consecutively, the Deaconess Hospital, and, a non-diabetics from the Mas were included 297 juvenile[68] cases under the age of twenty years, and 2102 adults All the juveniles were diabetic Division according to ages is shown in Table 96 The results of their study in 1935 should be compared with a similar series today

66 Keiding, Root and Marble Jour Am Med Assn, 150, 964, 1952

67 Waite and Beetham Loc cit, p 541

68 *Juvenile* in this section applies to patients under twenty years of age

Forty per cent of the diabetic patients were male and 60 per cent were female. With the non-diabetics, 51 per cent were male and 49 per cent were female. With the diabetic patients, hypertension with systolic pressure above 160 mm mercury was present in 486 cases and the diastolic was above 90 mm mercury in 465 of the 2002 diabetic patients. Diagnoses of tuberculosis were made in 54 of the diabetic group and of syphilis in 33. Among the non-diabetic patients diagnoses of tuberculosis were made in 30 cases and of syphilis in 29. The other diseases present included heart disease, gastro-intestinal disease, 57 cases of blood disorders, and a variety of other conditions.

In Table 97 are summarized the ocular abnormalities found in the entire series.

TABLE 97.—OCULAR ABNORMALITIES IN DIABETES

	4001 Eyes of Diabetics		*914 Eyes of Non-diabetics*	
	No.	*Per Cent*	*No.*	*Per Cent*
Wrinkles of posterior cornea	1040	26.0	96	10.5
Weakness of accommodation	165[69]	21.0		
Deep retinal hemorrhages	730[70]	18.0	34[71]	3.7
Waxy exudates in retina	420[70]	10.0	7[71]	0.8
Depigmentation of iris epithelium	258	6.0	21	2.0
Transitory refractive changes	246[73]	6.0		
Cataracta complicata	246	6.0	75	8.0
Iritis	52	1.3	12	1.3
Atrophy of optic nerve	27	0.6	4[71]	0.4
Homonymous hemianopsia	22	0.5		
Flocculi cataract, juvenile diabetics	22	0.5		
Glaucoma	21	0.5		
Argyll-Robertson pupils	20	0.5	2	0.2
Paralysis of extrinsic muscles	16	0.4	1	0.1
Tobacco amblyopia	14	0.3		

Transitory Refractive Changes.—The incidence of transitory refractive changes in diabetes ranges from 6 per cent in an unselected chronological series, to over 50 per cent in a selected freshly-treated group.[73] These changes are bilateral, have dramatic onset, and they may last from a few days to a few weeks.

Eyelids. The e[illegible] membranes of the [illegible] of similar age exc[illegible]

Cornea. In the cornea the frequency of arcus was the same in diabetics and non-diabetics, but a striking difference appeared in the frequency with which wrinkles involving Descemet's *membrane occurred*. Thus, in the diabetic such wrinkles were found in 26 per cent, whereas in non-diabetics they occurred in only 10.5 per cent. These wrinkles are invisible

[69] Only 759 eyes had accommodation measured.

[70] Only 3893 fundi of diabetics visible. (Fundi not seen in 108 eyes because of opacities in media.)

[71] Only 901 fundi of non-diabetics visible. (Fundi not seen in 13 eyes because of

selected group except that the patients were all alive at periods varying from ten to thirty-four years after the onset of diabetes. Careful study was made by x-ray examination of the arteries of the legs and pelvis, ophthalmoscopic examination by certified ophthalmologists and intensive blood studies. Among 247 patients a group of 37 patients under excellent and good control had developed neither marked retinal changes nor diabetic nephropathy over periods from ten to thirty-four years in duration In 134 of the 247 patients no hemorrhages or exudates were to be found in the retina In 103 patients whose diabetes had lasted from twenty to thirty-four years 3 of the 4 cases with excellent control had no retinal lesions whatever. Of the 54 cases with moderate to marked retinopathy all but 5 had had poor or only fair control, none had had excellent control No case

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than any other known factor such as duration or severity of diabetes in preventing or p ... the retina

Other Ocular ... quote freely and to extract ... m.[67] They examined, consecutively, the eyes of 2002 diabetics from the New England Deaconess Hospital, and, as a control group, examined similarly 457 non-diabetics from the Massachusetts General Hospital In this series were included 297 juvenile[68] cases under the age of twenty years, and 2162 adults All the juveniles were diabetic Division according to ages is shown in Table 96 The results of their study in 1935 should be compared with a similar series today

[66] Keiding, Root and Marble Jour Am Med Assn, 150, 964, 1952
[67] Waite and Beetham Loc cit, p 541
[68] Juvenile in this section applies to patients under twenty years of age

content or other eye complications such as diabetic retinitis. The average blood-sugar value for 100 true diabetics with complicated cataract was 234 mg

Flocculi occurred in 11 patients or 4 per cent of 297 juvenile diabetics They were always bilateral and in 7 cases were associated with fine iridescent crystals. In one half the patients presenting flocculi ...

100 grams approximately 9 5 milligrams calcium, 16 5 milligrams phosphorus, and 400 milligrams cholesterol The calcium content of the cataractous lens was 30 milligrams per cent, or three times the normal lens or blood value ...

phorus value was 19 7 milligrams per cent and the calcium-phosphorus ratio was somewhat higher than normal In the cataract of the diabetic on the other hand, the phosphorus value was much lower than in the cataract of the normal lens or of the lens of the non-diabetic individual, the average value being 6 2 milligrams per cent Therefore, the calcium-phosphorus ratio was correspondingly high The important point is brought out, therefore, that although in general the cataract forming in the eye of the diabetic appears chemically similar to the classical senile cataract, the phosphorus metabolism was markedly different This may be an important clue inasmuch as the relation between phosphorus and the dextrose metabolism in blood and tissues is already under intensive study

The development of cataracts in rats made diabetic either by alloxan or pancreatectomy was influenced first by the severity of the disease produced, the duration of the diabetes, and the age of the rats in the experiments of Rodriquez and Krehl [60] When cataracts developed in rats with severe diabetes both eyes were involved at approximately the same time On the other hand in rats with moderate diabetes cataracts were sometimes uni-

...ation in-
...roposed
...uptake

of glucose by the lens is impaired Since the lens depends upon glucose for a major portion of its energy, the total available energy is lowered beyond the critical point necessary for maintaining transparency The lens also depends on other constituents of the blood for an alternate source of energy

[59] Cates and Hunt New England Jour Med, *212*, 463, 1935
[60] Rodriguez and Krehl Yale Journal of Biology and Medicine *23*, 103, 1951
[61] Patterson Diabetes, *5*, 93, 1956

with the ophthalmoscope, but were seen with the aid of the slit-lamp and corneal [illegible]

in the [illegible]

51 per [illegible]

Pupi[illegible]

betic eyes [illegible]

out histor[illegible]

fluid. Th[illegible]

syphilis is [illegible]

and Fair[75] who report cases showing Adie's syndrome[76] with pupillary reactions resembling those of the Argyll-Robertson pupil, not due to syphilis

Lens.—In the lens two types of abnormality stood out in the series of Waite and Beetham, refractive changes and lenticular opacities. The first consisted of transitory refractive changes occurring with blurred vision in 123 cases. Fifty-eight patients were under fifty years of age. Although the explanation for these changes was not clear, they must be due to changes in the index of refraction of the lens nucleus, resulting from changes in salt retention and osmotic interplay associated with rapid shifts in blood sugar. Counting all types, lens opacities were found in 1732 lenses among 3407 diabetic eyes, an incidence of 50 per cent. In the non-diabetics over twenty years of age, the incidence was 57 per cent. Shepardson and Crawford[77] report lenticular opacities in 54 per cent of 68 diabetic patients ranging in age from eighteen to seventy-nine years, the average age being fifty-four years

Cataracta complicata[78] has usually been regarded in the literature as more frequent in diabetics than in non-diabetics. In general, the frequency of complicated cataracts increased with the duration of the diabetes Thus, of patients with diabetes of less than one year's duration, only 2 per cent had s[illegible]

three[illegible]

years[illegible]

cent h[illegible]

occurred in 10 per cent of the cases. However, in this last group the average age was 61 8 years as compared with an average age between forty and fifty-five years for the other age groups No definite correlation was found between complicated cataract and the amount of insulin given, blood-sugar

[74] Duke-Elder Textbook of Ophthalmology, St Louis, C V Mosby Co, *1*, 562 1934

[75] Perry, Wartis, Ricardo and Fair Arch Ophth, *19*, 68, 1938

[76] [illegible] New York State [illegible]

Optic Pathways.—In the optic pathways three types of abnormalities were observed by Waite and Beetham; (1) sector defects, 48 cases, (2) homonymous hemianopsia, 24 cases; and (3) toxic amblyopia, 14 cases The susceptibility of older diabetics to tobacco poisoning should be emphasized according to Waite

"The prognosis is good if the patient will omit tobacco completely, provided optic atrophy has not already set in Recovery is complete in several months in light poisoning but takes longer in severe cases. Alcohol tends to keep the recovery in check, and it should be omitted also Free elimination by bowel, bladder and sweat glands, and the use of Vitamin B in the form of yeast are indicated Sedatives should be used the first few weeks to tide the patient over a very difficult period

"The exact explanation of what toxic agents produce tobacco amblyopia is still lacking (nicotine, CO, *etc*.). It is thought that the toxic agents poison the retinal ganglion cells, rather than the fibers of the optic nerve itself" (Waite)[80]

[80] Personal Communication

The quantity of B substances is determined by other organs, notably the liver.

Isolated rat lenses removed glucose from the medium at a constant rate for several hours, but lenses from rats with diabetes of one week's duration have an uptake of glucose of less than half normal.

Lipemia Retinalis.—Disturbances in lipid metabolism of marked degree are often induced by diabetic acidosis, and are characterized by chemical lipemia, consisting principally of neutral fat, by hypercholesterinemia and by a variable degree of lactescence of the separated serum. In the 18 cases of acidosis and coma reported by Tuller[82] *et al.* from the New England Deaconess Hospital, one had lipemia retinalis. Diabetic coma was accompanied by greater elevations of serum cholesterol and of serum lipoproteins of S_f 0–11, 12–20, 20–100 and 100–400 classes than were less severe degrees of acidosis. However, the variability in the relationship of these components indicated a basic lipid disturbance not explained entirely as a simple consequence of the degree of ketosis. The creamy appearance of the plasma is accompanied by a salmon-pink color which makes arterioles and veins in the retina indistinguishable from one another. Under the influence of insulin, the lipemia may clear within a few hours

In addition to the two cases reported by Gray and Root,[83] 11 other patients have been observed at the New England Deaconess Hospital. Case 29387, and our most recent case, 39428, eighteen and nineteen years of age respectively, entered in acidosis with plasma cholesterol of 1410 and 1700 mgs Improvement was rapid. Multiple xanthomata were present in palms and on elbows. Seven cases occurring among 108 cases of diabetic coma were reported by Baker [84]

Marble and Smith[85] made serial determinations of the total blood fat, total cholesterol, ester cholesterol and phospholipins in 2 of our cases (12383 and 12384) One case had an initial blood fat of 14.1 and the other of 7.5 per cent The greatest increase took place in the fatty acid fraction. Next

Carsagno,[88] and Kalinowski.[89]

The ages of development in 59 of the 69 cases of lipemia retinalis were less than twenty years in 24 cases, between twenty and thirty years in 22 cases, and between thirty and forty years in only 3 instances

Formerly lipemia retinalis was regarded as a reflection of a hopelessly

years to die of coronary occlusion In general, the prognosis is good if diet and insulin are properly used

[82] Tuller, Mann, Schertenleib, Roehrig and Root Ibid, *3*, 279, 1954
[83] Gray and Root Jour Am Med Assn, *80*, 995, 1923
[84] Baker Arch Int Med, *58*, 373, 1936
[85] Marble and Smith Arch Ophthal, *15*, 86, 1936
[85a] Franklin and Weissman Ann Int Med, *46*, 413 1957
[86] Kauffmann Ibid, *29*, 693, 1943
[87] Lefkovitz and Young Ann Int Med, *32*, 755, 1950
[88] Carsagno and Steiger Amer Jour Med Sci, *221*, 379, 1951
[89] Kalinowski and Miles Brit Med Jour, *2*, 661, 1953

cases must be interpreted with due consideration not only for the actual incidence of new cases of tuberculosis each year but with recognition of the

reported cases are under forty-three years of age However, the high mortality among adults from 50 years onward reflects a decrease in the effectiveness of treatment and increased case finding Great variation exists in this case rate for newly reported active, and probably active, tuberculosis in the United States and territories The x-ray case-finding programs have increased so that in the year 1955, more than 16,000,000 perople were examined, or slightly over 10 per cent of the population The fact that less than 25 per cent of the newly reported cases were minimal and approximately 35 per cent far advanced in the years 1952–1954, indicates great need for intensified effort.

B COEXISTENT TUBERCULOSIS AND DIABETES

Avicenna (980–1027) first noted the frequent association of diabetes and pulmonary tuberculosis,[3,4] and the subject has continued to interest students of diabetes ever since The incidence of pulmonary tuberculosis in diabetic patients treated with the high caloric diet in 1898–1914 was about the same as when the diabetes was treated with under-nutrition prior to the discovery of insulin, whereas the rate of development of pulmonary tuberculosis in relation to the years of exposure fell to one-third during the years following the use of insulin The susceptibility of the uncontrolled diabetic to tuberculosis deserves continued emphasis A total of 886 cases was recognized among 32,148 diabetics between 1898 and January 1, 1951 Earlier recognition of tuberculosis will require the extension on a large scale of case-finding mass surveys as recommended by the Tuberculosis Control Division of the U S Public Health Service,[5] and completed among diabetics in Philadelphia [6]

statistics in a somewhat later period when the segregation of tuberculous from nontuberculous patients had become more general However, figures for the frequency of pulmonary tuberculosis in diabetics are given by Thiery[7] in Paris, Ponteva[8] and Vartiainen[9] in Finland, varying from 18 8 to 40 per cent of all diabetic deaths Wiener and Kavee[10] found among 218

[3] Grafe Diabetes und Tuberkulose, Stuttgart, Thieme, 5, 1948

[4] Root and Bloor Am Rev Tuberc, 39, 714, 1939, Am Jour Med Sci, 200, 53, 1940

[5] Hilleboe and Morgan Mass Radiography of the Chest, Chicago, 1945

[6] Boucot Cooper Dillon, Meier and Richardson Tuberculosis Among Diabetics, The Philadelphia Survey, Am Rev Tuberc, 65, 2, 1952

Thiery Jour Am Med Assn, 104, 330, 1935

[8] Ponteva Acta Med Scan, Suppl, 88, 1, 1938

[9] Vartiainen Acta Med Scan, 118, 579, 1944

[10] Wiener and Kavee Am Rev Tuberc, 34, 179, 1936.

Chapter 23

TUBERCULOSIS

HOWARD F. ROOT, M.D.

A INTRODUCTION

Present Tendencies in Tuberculosis.—The danger of tuberculosis for the diabetic patient depends first upon the prevalence of tuberculosis in the community in which he lives and then upon his own individual susceptibility, especially as the latter is affected by the control of his diabetes. In continental United States[1] the rate of decline in tuberculosis deaths has been greater in the past decade than in earlier years, but there has not been a comparable fall in the number of newly reported cases of tuberculosis (See Figure 27)

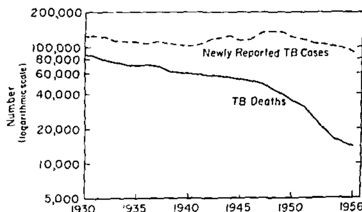


FIG 27 —Newly reported tuberculosis cases and tuberculosis deaths, United States, 1930–1956

The decline in deaths attributed to tuberculosis is an indication of progress in one aspect of the control of this disease However, the continued high level of new cases, together with the great number of treated cases released in the community *while still undergoing treatment*, and the large number of non-hospitalized cases,[2] indicate the continuing need for constant work in detection and control It is true that the data on newly reported

[1] Tuberculosis Chart Series Division of Special Health Services, U S Dept Health, Education and Welfare, May 1957, Publication No 534

[2] Blomquist, Am Jour Pub Health, *46*, 149, 1956

there were 3 reported deaths from tuberculosis and 25 reported deaths from diabetes mellitus

Changing Mortality Rates.—The longer the duration of diabetes the greater the opportunity for contact with active cases and therefore of infection The less well controlled the diabetes, the greater the susceptibility to infection becomes All students have agreed that tuberculous patients [illegible]

[illegible]

the death rate from tuberculosis in the industrial population has been reduced more than 90 per cent. The provision of sufficient sanatorium beds for active cases removes the infective cases from the community Another public health measure is the extended use of pneumothorax treatment which [illegible] readily [illegible] tients [illegible] posed *to infection*

TABLE 98.—PULMONARY TUBERCULOSIS—BOSTON, MASSACHUSETTS

Resident Cases and Case Rates, Deaths and Death Rates—1950–1956

Year	*No Cases*	*Case Rate**	*No Deaths*	*Death Rate**	*Deaths Over 65 Years*
1950	823	108.0	329	41.1	89
1951	752	102.3	301	37.4	144
1952	770	95.3	270	33.4	80
1953	764	94.2	210	25.9	103
1954	796	97.8	195	24.0	82
1955	722	88.4	152	18.6	57
1956	596	72.7	141	17.2	52

* Per 100,000

DIABETES MELLITUS—BOSTON, MASSACHUSETTS

Resident Deaths and Death Rates—1950–1956

Year	*Number of Deaths*	*Death Rate**	*Deaths Over 65 Years*
1950	210	26.6	145
1951	233	29.0	144
1952	216	26.7	150
1953	172	21.2	113
1954	140	17.2	97
1955	156	19.1	108
1956	148	17.1	101

* Per 100,000

The death rates from diabetes and pulmonary tuberculosis in Boston reached almost the same figure in 1956 In Table 98 are given data supplied through the courtesy of the Health Commissioner of the City of Boston,

Statistical Bulletin, Metropolitan Life Insurance Company, 38, 11, 1957

cases of pulmonary tuberculosis and diabetes observed at the Montefiore Hospital in New York and its sanatorium that the incidence of diabetes mellitus among tuberculous patients in 1944 was 14 2 per cent This high percentage is probably due, as Wiener and Kavee stated, to the fact that at the Montefiore Hospital there is a special interest in diabetes and the population is almost exclusively Jewish

Among 51,705 nondiabetic autopsies an incidence of active, not necessarily fatal tuberculosis of 22.9 per cent was found by Root,[11] whereas among 1121 diabetic autopsies active tuberculosis was present in 28 4 per cent. As an actual cause of death Bell[12] found tuberculosis in 3.7 per cent of 1214 diabetic autopsies Considering that the two diseases occur in association with less frequency than either one alone, it appears that tuberculosis is about 2 or 3 times as frequent at autopsy as would be expected in diabetics. The incidence of pulmonary tuberculosis in 1,138 necropsies at the London Chest Hospital, reported by Gloyne,[13] was 1.4 per cent Neogy and Roy[14] found an incidence of 3 3 per cent of tuberculosis among 1,882 diabetics in the Jadabpur Hospital. The chief criticism of autopsy figures depends upon the fact that until recently diabetics examined at autopsy were apt to be patients with diabetes of short duration, who died of coma or an acute infection before they had lived long enough with diabetes to demonstrate whether or not they would have developed tuberculosis. Among 135 patients with onset of diabetes in childhood, deaths occurring between 1946 and 1950, were due to pulmonary tuberculosis in 10 per cent of the cases [15] Tuberculosis is still second only to cardio-renal disease as a later cause of death in juvenile diabetes, although in adults it has fallen to 1 per cent of total deaths, and in the first nine months of 1957, not a single death from tuberculosis was reported among our diabetics.

The Philadelphia Survey[16] included probably 30 per cent of the known diabetics of that city Three-quarters of the 3,106 diabetics studied were above the age of fifty, and females contributed 70 per cent. Tuberculosis was present in 8 4 per cent, whereas among a group of 71,767 apparently healthy Philadelphian industrial workers the prevalence of tuberculosis was found to be 4 3 per cent Under the age of forty, patients with diabetes of less than ten years' duration showed only 3 2 per cent active tuberculosis in contrast with 11 4 per cent of those whose diabetes was of more than

of 0 17 per cent At the same time that the people were having their x-rays, the diabetes demonstration unit offered tests of urine and blood for sugar, and 2,100 of the 6,000 were given these tests Of this number, 18 new diabetics were discovered, or about 0 88 per cent (5 times the discovery rate of tuberculosis) It is of interest that in this same community in 1947

[11] Root New England Jour Med , *210*, 8, 1934
[12] Bell: Proc Am Diabetes Assn , *10*, 64, 1950
[13] Gloyne Brit Med Jour , *2*, 163, 1938

it p 563

with the observed more rapid development of tuberculous processes in the diabetic. They emphasize the seriousness of prognosis. Twenty per cent of the cases died in less than one year. Tuberculosis outside the lungs and especially of the serous surfaces is rare in diabetes, except in combination with pulmonary tuberculosis.

A striking feature in the tissues of diabetic patients is the remarkable alteration of the fat content of certain organs. The removal of fat from one tissue and its deposit in another have been correlated with certain well-recognized changes in the severity and intensity of diabetes. It is of some interest, therefore, to know whether or not the lipid content of lung tissue could be related in any way to the resistance of the diabetic lung to tuberculin infections. Analyses of lungs removed at autopsy at the Deaconess Hospital are reported by Root and Bloor.[25] Although few figures are available for the lipid content of lung tissue in animals or human beings, certain comparisons were made. Root and Bloor listed the clinical data and analyses of 26 diabetic and 2 non-diabetic patients together with the values for phospholipid and cholesterol content of the lungs. Among 12 cases whose phospholipid value exceeded 1.10 grams per 100 grams wet tissue, 5 showed evidences of tuberculous infection chiefly healed. One patient with a value of 2.44 grams had a fatty liver and indeed fat-filled livers with lipoidosis of the spleen were noted in 4 cases. Fifteen of the 26 diabetics had cholesterol values of 0.35 grams per cent or higher and in this group we find 6 of the patients with healed apical tuberculosis and again almost constant arteriosclerosis and fatty livers. A number of patients, however, had low phospholipid values, a fact which may well be considered together with the observation that diabetic cataracts also show a low phosphorus content as described by Carey and Hunt.[26]

The cultural and metabolic characteristics of the tubercle bacillus have [illegible]

salicylic acid are summarized. References to the many studies of the enzymatic systems in the bacillus and the structural elements of the organism are given. Glycerol occupies a special position as a source of carbon nutrition, especially in cultures of the human and avian strains. Its rate of consumption varies with the virulence of the strain. In [illegible]

glucose

alone

of bacilli utilize glucose, mannose, fructose, arabinose, galactose, xylose and maltose, but not lactose. There is an interdependence between carbon compounds, mineral and nitrogen elements. Thus, among the mineral elements favorable to growth, iron is important and its influence is more

[25] Root and Bloor. Loc. cit., p. 563.
[26] Carey and Hunt. New England Jour. Med., *212*, 463, 1935.
[27] Drea and Andrejew. Metabolism of the Tubercle Bacillus, Springfield, Illinois, Charles C. Thomas, 1953.

Dr. John Cauley. Over the age of 65 years diabetic deaths outnumbered deaths from tuberculosis 2 to 1 in 1955 and 1956.

Deaths ascribed *to diabetes are now classified according to the Sixth* Revision of the International List of Diseases and Causes of Death This classification gives a materially lower incidence of diabetes than does the Fifth Revision. The effect of the Sixth Revision is shown in a table issued by the National Office of Vital Statistics [19] This table compares the classifications of deaths for the two years, 1949, and 1950. For tuberculosis, the number by the Sixth Revision was 96 per cent of the total, as classified by the Fifth Revision. For diabetes, this proportion is 57 per cent.

The incidence of diabetes in tuberculosis sanatoria is increasing In Massachusetts, whereas 1 person in the state out of 200 to 250 had diabetes, in 1934, 0.7 per cent of the sanatoria population had diabetes. This percentage is growing because, according to Dr. William H. Weidman, Director, Division of Tuberculosis, it was 3.8 per cent in December 1956, in 16 Massachusetts Sanatoria for pulmonary tuberculosis. Among 3,178 patients admitted to Uncas-on-Thames Tuberculosis Hospital between 1937 and 1950, 68 or 2.1 per cent had diabetes.[20]

C. PATHOLOGY AND BACTERIOLOGY OF TUBERCULOSIS IN *DIABETES*

It is easy to point out certain peculiarities of tuberculosis in diabetes, but difficult to explain them Root[21] tabulated 126 autopsies upon tuberculous diabetics including 15 cases from the New England Deaconess Hospital

[illegible]

groups. (1) thin, insulin-sensitive, (2) fat, hypertonic, insulin-resistant,

[illegible]

findings of 48 diabetic and 48 non-diabetic patients with pulmonary tuberculosis Thick pleural adhesions of both lungs were twice as frequent in non-diabetics as in diabetics This comparative lack of adhesions is an important explanation of the fact that in diabetic patients collapse therapy can often be carried out with excellent results This fact also is consistent

[illegible] *36*, December 3, 1951

[19] Grate Loc cit p [illegible]
[20] Wiener and Kavee. Loc cit p 563

The degree of glycosuria and the essential severity of the diabetes show the same range of variation as is found in other diabetics. When a diabetic is not doing well without an apparent cause, tuberculosis should be suspected The fact that this old rule holds indicates that with advancing tuberculosis the effect upon the diabetes may be unfavorable On the other hand, the opposite effect is frequently seen When the tuberculosis is advancing rapidly, emaciation is occurring, then the diabetes may become so amenable to treatment that the glycosuria completely disappears, and a small dose of insulin may provoke a serious hypoglycemia

TABLE 99 —SIX HUNDRED AND EIGHTY-SIX CASES OF COMBINED TUBERCULOSIS AND DIABETES

Years of Onset	*Tuberculosis, Number of Cases*	*Diabetes, Number of Cases*
0–9	5	31
10–19	44	82
20–29	116	91
30–39	122	124
40–49	98	131
50–59	156	142
60–69	105	68
70–79	36	14
80 & up	4	0
TOTAL	686	686

The blood sugar in tuberculous diabetics exhibits about the same variations as are found in the non-tuberculous except when, due to wide dissemination of the infection, the functions of the liver or of the adrenals are impaired The cholesterol of the blood oftentimes may fall to a low level in tuberculous patients with cachexia and serve as a warning of impending hypoglycemia Cases 2148 and 11471 in this series had cholesterol values of 78 and 72 mg per 100 cc respectively Severe hypoglycemia occurred with only 15 units of insulin in Case 11471 Both patients died within a few days

Variations in insulin requirement were no greater in our tuberculous than in our non-tuberculous cases It is difficult to find a form of tuberculosis typical of diabetes

The onset of tuberculosis in the diabetic is no more insidious than in the non-diabetic although the rapidly progressive form of tuberculosis is most frequently described In general prognosis is as good as in non-diabetics The most frequent type of onset was catarrhal, bronchitic and insidious. Actually, comparison with the series from the Trudeau Sanatorium analyzed by Lawrason Brown reveals more cases in his series with proven tuberculosis without physical signs than are found among the diabetics The usual physical signs, râles and dulness, are found in diabetics if we but examine them frequently enough

E ROENTGENOGRAMS IN DIABETES

At present we plan to continue the practice of securing a roentgen-ray examination of the lungs with repetition annually, especially in youthful

pronounced with a rich glycerol medium. Glycerol is present in the human body chiefly in the combined form of fat, but it is noteworthy that a certain amount must be free at times and in periods of fat catabolism, as in diabetic acidosis and coma, the amounts of glycerol set free or the rate at which it is set free must be greatly altered. In acidosis there is also an increase in protein catabolism.

Immunity in Diabetes.—Vaccination with BCG has been practiced much more generally in Europe than in the United States. No definite information seems to be available with respect to any large diabetic group. Malmros[24] describes vaccination with BCG of a large part of the population in Orebro, Sweden. Among the population generally all non-reactors had been vaccinated and at the date of his article 22,413 had been so treated including 8,040 new born and 7,830 children. Only 1 case of tuberculosis had developed.

Native immunity in contrast to acquired immunity must vary greatly in different individuals. In diabetics as a group it is not low before the development of diabetes if one considers that (1) deaths from tuberculosis in [illegible] tuberculous diabetics are [illegible] nce of healing shown by [illegible]

does the immunity conferred by the healing of a primary infection suffice for the protection of the diabetic. Something occurs after development of diabetes, whether it is by reason of weight loss, or by reason of acidosis or other chemical changes, which reduces his normal resistance. The influence of diabetes is also indicated by the fact that control of the diabetes by active treatment does favor improvement of the tuberculosis. The low resistance of diabetics to tuberculosis does not apply to other pulmonary infections.

D. DEVELOPMENT OF TUBERCULOSIS IN THE DIABETIC

Clinically, it is an outstanding fact that in the past the discovery of tuberculosis in a diabetic in a truly incipient stage has been almost unknown. The hopeless prognosis and rapid progression of tuberculosis in the diabetic were probably due largely to the extraordinarily tardy diagnosis, usually established when the tuberculosis was so far advanced that nothing but a short course could have been expected. In our 686 cases there were only 28 in which the lesion was incipient according to the standards established by the American Sanatorium Association and the National Tuberculosis Association. The comparative ages of onset of tuberculosis and diabetes are shown in Table 99.

Eighty per cent of the 686 cases had been more than 5 per cent overweight before the onset of diabetes. Great loss of weight was an outstanding feature. The average loss of weight for 219 cases was 42 pounds and in 19 cases the loss of weight was in excess of 75 pounds each.

[24] Malmros. British Med. Jour., *1*, 1129, 1948.

TABLE 100.—LOBECTOMY AND PNEUMONECTOMY IN DIABETIC PATIENTS WITH TUBERCULOSIS

A. Lobectomy

Case No.	*Sex*	*Onset of Diabetes* *Age*	*Onset of Diabetes* *Date*	*Insulin Units*	*Date of Operation*	*Follow-up Date L. or D.*
9018	F	13	III '30	64	Feb '45	L. Sept '57
11225	F	34	VI '32	30	Nov '42	D. Aug '46
11617	M	33	IX '32	78	Sept '50	L. June '55
12997	F	6	X '33	80	Feb '45	D. Dec '46
13237	M	27	XII '33	72	Feb '50	L. Feb '58
15381	M	27	I '36	66	Mar '48	L. May '56
19241	F	49	V '40	76	Nov '50	L. Aug '57
20479	F	34	VI '32	50	Nov '42	D. Aug '46
21421	F	52	IX '41	0	Apr '42	L. Dec '54
23033	M	15	II '41	82	Oct '50	L. May '58
23313	F	18	XII '39	94	Mar '45	L. Sept '57
23521	M	23	I '37	92	Nov '50	L. Apr '57
24674	F	41	VII '43	34	Mar '44	L. Oct '57
26016	M	63	XI '42	20	Mar '44	D. Oct '45
26614	M	54	XII '44	12	Aug '45	D. Dec '47
31388	M	55	VII '39	24	Sept '47	L. May '57
31950	M	40	'32	68	Dec '47	L. Feb '56
34801	F	38	I '29	68	May '49	D. July '51
35570	M	42	I '44	68	Oct '49	L. Aug '57
35762	M	31	I '45	60	Oct '50	L. Apr '58
36760	M	9	X '47	98	Jan '50	L. Apr '58
37655	M	33	XI '39	112	Dec '50	L. Jan '57
38592	F	51	V '51	60	May '51	L. Aug '57
8570	M	11	XI '29	90	Jan '52	L. July '57
10084	F	20	V '29	30	May '52	D. May '52
12434	F	11	IX '33	54	Feb '53	L. Oct '57
19390	M	36	VIII '40	10	Oct '55	L. May '57
19871	F	37	VIII '38	68	June '52	L. Mar '57
23616	M	40	X '43	94	Apr '52	L. Mar '56
25605	M	25	IV '44	44	Dec '53	L. Oct '57
27288	F	24	VI '45	74	May '54	L. Nov '57
27495	F	49	XI '37	74	Jan '53	L. Feb '53
28084	M	17	II '46	88	Dec '53	L. Aug '57
31001	F	48	III '46	60	Nov '54	L. Aug '57
32146	M	18	XI '47	88	June '51	L. Nov '57
35762	M	31	I '45	66	Oct '51	L. Apr '58
39012	F	52	VII '48	72	July '51	L. Nov '56
39204	M	23	VI '46	110	June '52	L. Feb '55
40545	M	55	I '45	82	June '52	L. Oct '55
41391	F	45	X '52	0	Oct '52	L. Apr '54
43366	F	16	VII '45	100	Dec '53	L. Mar '54
43428	F	66	XII '53	20	Jan '54	L. July '56
43497	F	33	II '53	40	Jan '54	L. Jan '54
43694	M	26	III '50	84	Mar '54	L. Aug '56

B. Pneumonectomy

Case No.	*Sex*	*Onset of Diabetes* *Age*	*Onset of Diabetes* *Date*	*Insulin Units*	*Date of Operation*	*Follow-up Date L. or D.*
6593	M	19	I '28	34	Dec '42	L. July '57
16858	M	4	VII '30	90	Oct '46	L. Nov '57
27082	M	24	X '25	62	Sept '46	L. Sept '57
29407	F	11	V '46	98	Aug '50	L. Nov '57
32295	M	39	X '33	40	Feb '48	D. Nov '49
34928	F	48	III '48	14	May '49	D. July '50
37684	M	56	XI '50	0	Nov '50	D. Dec '50
15508	M	37	XI '32	6	Dec '51	L. Apr '57
23009	F	51	VII '42	36	June '55	L. Jan '56
32390	F	50	VII '37	6	Mar '52	D. May '52
39112	M	41	VII '49	26	July '51	L. June '56
41666	M	45	VIII '49	60	Jan '53	D. Jan '53

The results in the cases operated upon give reason to believe that this type of surgery performed in properly selected patients may afford another ray of hope for the diabetic patients who develop pulmonary tuberculosis.

diabetics, in those who have had coma and in cases with known exposure to tuberculosis Every diabetic admission to the New England Deaconess Hospital has an *x*-ray examination of the chest. In our first series of 1659 consecutive examinations, 42 per cent of diabetic children in the first decade and 70 per cent of the cases in the second decade showed calcification of the tracheobronchial glands. Positive skin tests with tuberculin varied from 30 to 45 per cent. Among 1430 diabetic children 21 subsequently developed tuberculosis, an incidence of 1 5 per cent or more than 10 times the incidence in 5,000 Massachusetts school children Malins[29] found twice the incidence of tuberculosis in a mass *x*-ray survey among diabetics as among the general population of Birmingham, England. In a review of diabetic deaths he found 12 out of 17 deaths under the age of forty due to tuberculosis. In 1957, he reported 1 death only in a series of 80 patients

In the Boston Chest *X*-ray Survey,[30] 528,941 films satisfactory for interpretation were done in a few weeks, 4,122 cases of tuberculosis were diagnosed, of whom 67 4 per cent were judged as minimal However, 1,152 cases were moderately advanced and 87 were far advanced. In our series of 1659 diabetics, roentgenograms of the chest were positive in 2 4 per cent.

less advanced lesions 11 per cent of the cases. No special type of diabetic lesions was observed, although exudative, pneumonic types with cavitation frequently developed in patients with evidences of old infection In 49 cases tuberculosis developed after the age of sixty years. Processes apparently latent for much of a lifetime developed activity after the onset of diabetes Pleurisy with effusion and progression to death with cavitation in one case and death from tuberculous meningitis in the second occurred in 2 diabetic men, aged seventy-five and sixty-five years respectively. The rate of progression can be measured best by roentgen-ray examination.

F LOBECTOMY AND PNEUMONECTOMY

In Table 100
ing pulmonary
instances and

of pulmonary tuberculosis in our diabetic patients have undergone such surgery at the New England Deaconess Hospital Surgical recovery occurred in each case Twenty-three of the 56 cases were females, and 13 of the 56 patients had the onset of diabetes before the twentieth year, the youngest at the age of 6 8 years In this young group the duration of diabetes from its onset to the time of operation for pulmonary tuberculosis varied from three to twenty years In the older group the tuberculosis was

[29] Malins Clin Jour, *80*, 319, 1951
[30] Cauley New England Jour Med, *243*, 631, 1950

TABLE 100.—LOBECTOMY AND PNEUMONECTOMY IN DIABETIC PATIENTS WITH TUBERCULOSIS

A Lobectomy

Case No	*Sex*	*Onset of Diabetes* *Age*	*Onset of Diabetes* *Date*	*Insulin Units*	*Date of Operation*	*Follow-up Date L or D*
9018	F	13	III '30	61	Feb '45	L Sept '57
11225	F	34	VI '32	30	Nov '42	D Aug '46
11617	M	33	IX '32	78	Sept '50	L June '55
12907	F	6	X '33	80	Feb '45	D Dec '46
13237	M	27	XII '33	72	Feb '50	L Feb '58
15381	M	27	I '36	66	Mar '48	L May '56
19241	F	49	V '40	76	Nov '50	L Aug '57
20479	F	31	VI '32	50	Nov '42	D Aug '46
21421	F	52	IX '41	0	Apr '42	L Dec '54
23033	M	15	II '41	82	Oct '50	L May '58
23343	F	18	XII '39	94	Mar '45	L Sept '57
23521	M	23	I '37	92	Nov '50	L Apr '57
24674	F	44	VII '43	34	Mar '44	L Oct '57
26016	M	63	XI '42	20	Mar '44	D Oct '45
26614	M	54	XII '44	12	Aug '45	D Dec '47
31388	M	55	VII '39	24	Sept '47	L May '57
31950	M	40	'32	68	Dec '47	L Feb '56
34801	F	38	I '29	68	May '49	D July '54
35570	M	42	I '44	68	Oct '49	L Aug '57
35762	M	31	I '45	60	Oct '50	L Apr '58
36760	M	9	X '47	98	Jan '50	L Apr '58
37655	M	33	XI '39	112	Dec '50	L Jan '57
38592	F	54	V '51	60	May '51	L Aug '57
8570	M	11	XI '29	90	Jan '52	L July '57
10084	F	20	V '29	30	May '52	D May '52
12334	F	11	IX '33	54	Feb '53	L Oct '57
19390	M	36	VIII '40	10	Oct '55	L May '57
19871	F	37	VIII '38	68	June '52	L Mar '57
23616	M	40	X '43	94	Apr '52	L Mar '56
25605	M	25	IV '44	44	Dec '53	L Oct '57
27288	F	24	VI '45	74	May '54	L Nov '57
27495	F	49	XI '37	74	Jan '53	L Feb '53
28084	M	17	II '46	88	Dec '53	L Aug '57
31001	F	48	III '46	60	Nov '54	L Aug '57
32146	M	18	XI '47	88	June '51	L Nov '57
35762	M	31	I '45	66	Oct '54	L Apr '58
39012	F	52	VII '48	72	July '54	L Nov '56
39204	M	23	VI '46	110	June '52	L Feb '55
40545	M	55	I '45	82	June '52	L Oct '55
41391	F	45	X '52	0	Oct '52	L Apr '54
43306	F	16	VII '45	100	Dec '53	L Mar '54
43428	F	66	XII '53	20	Jan '54	L July '56
43497	F	33	II '53	40	Jan '54	L Jan '54
43694	M	26	III '50	84	Mar '54	L Aug '56
B Pneumonectomy						
6593	M	49	I '28	34	Dec '42	L July '57
16888	M	4	VII '30	90	Oct '46	L Nov '57
27082	M	24	X '25	62	Sept '46	L Sept '57
29407	F	11	V '46	98	Aug '50	L Nov '57
32295	M	39	X '33	40	Feb '48	D Nov '49
34928	F	48	III '18	14	May '49	D July '50
37681	M	56	XI '50	0	Nov '50	D Dec '50
15508	M	37	XI '32	6	Dec '51	L Apr '57
23009	F	51	VII '42	36	June '53	L Jan '56
32390	F	50	VII '37	6	Mar '52	D May '52
39412	M	31	VII '49	26	July '51	L June '56
41666	M	45	VIII '49	60	Jan '53	D Jan 53

The results in the cases operated upon give reason to believe that this type of surgery performed in properly selected patients may afford another ray of hope for the diabetic patients who develop pulmonary tuberculosis

diabetics, in those who have had coma and in cases with known exposure to tuberculosis. Every diabetic admission to the New England Deaconess Hospital has an x-ray examination of the chest. In our first series of 1650 consecutive examinations, 42 per cent of diabetic children in the first decade and 70 per cent of the cases in the second decade showed calcification of the tracheobronchial glands. Positive skin tests with tuberculin varied from 30 to 45 per cent Among 1430 diabetic children 21 subsequently developed tuberculosis, an incidence of 1.5 per cent or more than 10 times the incidence in 5,000 Massachusetts school children. Malins[39] found twice the incidence of tuberculosis in a mass x-ray survey among diabetics as among the general population of Birmingham, England. In a review of diabetic deaths he found 12 out of 17 deaths under the age of forty due to tuberculosis. In 1957, he reported 1 death only in a series of 80 patients

In the Boston Chest X-ray Survey,[40] 528,941 films satisfactory for interpretation were done in a few weeks; 4,122 cases of tuberculosis were diagnosed, of whom 67.4 per cent were judged as minimal. However, 1,152 cases were moderately advanced and 87 were far advanced. In our series of 1659 diabetics, roentgenograms of the chest were positive in 2.4 per cent.

Roentgenograms of the lungs in 87 diabetics with active tuberculosis also showed multiple areas of calcification indicating long-standing and healed areas of infection Moderate and advanced processes made up 89 per cent, less advanc

lesions was

frequently

cases tuberculosis developed after the age of sixty years. Processes apparently latent for much of a lifetime developed activity after the onset of diabetes Pleurisy with effusion and progression to death with cavitation

F LOBECTOMY AND PNEUMONECTOMY

In Table 100 are summarized the records of 56 patients in whom advancing pulmonary tuberculosis was treated by surgical removal of one lobe in 44 instances and total pneumonectomy in 12 cases The indications for the

of pulmonary tuberculosis in our diabetic patients have undergone such surgery at the New England Deaconess Hospital Surgical recovery occurred in each case Twenty-three of the 56 cases were females, and 13 of the 56 patients had the onset of diabetes before the twentieth year, the youngest at the age of 6 8 years In this young group the duration of diabetes from its onset to the time of operation for pulmonary tuberculosis varied from three to twenty years In the older group the tuberculosis was

39 Malins Clin Jour, 80, 319, 1951
40 Cauley New England Jour Med, 243, 631, 1950

Sample diets for use with tuberculosis patients on the basis of a patient weighing 132 pounds may be classified as follows:

TABLE 101.—DIETS FOR TUBERCULOUS DIABETICS[31]

	Carbohydrate, grams	*Protein, grams*	*Fat, grams*	*Calories*
1 Standard diet	150	80	100	1820
2 Surgical diet—before operation	200	75	70	1730
—day of operation	100	20–30	40–50	840–970
3 Diet to increase weight	250	100	120	2480

Insulin. [illegible]

breakfast. In case of exposure to an open case of tuberculosis, insulin should never be omitted unless the exposure is known to be slight, weight and general health are normal, and the urine and blood sugar are normal with an adequate diet. Among 144 cases the average insulin prescribed at discharge from the hospital was 28 units. The smallest daily dose was 2 units and the maximum 83 units. The distribution of the injections in various areas is important in order to avoid induration and consequent loss of efficiency of insulin. Atrophy of subcutaneous fat has not been noted in tuberculous cases. On the average, tuberculous cases do not require more insulin than non-tuberculous. These results indicate that the harmful effects of tuberculosis on diabetic tolerance are easily exaggerated. During periods of high fever and toxemia the insulin requirement will usually be increased. As a rule, however, when careful dietary treatment and adjustment of the insulin dose are carried out so that wastage is avoided, no evidence of a great increase in the insulin requirement appears.

Hypoglycemia is not rare in tuberculous diabetics undergoing dietary and insulin treatment. Patients with advanced tuberculous lesions and acute toxemia from pneumonia or generalized tuberculosis seem especially liable to insulin reactions. If Addison's disease is present, hypoglycemia may easily develop
adrenals is ab
in Case 11419
years. On Oc
was 280 mg
entered the h
non-protein nitrogen was 40 mg, and the cholesterol of the blood was 70 mg. per 100 cc. Insulin was immediately stopped and his diet increased to 220 grams carbohydrate. Two weeks later he was apparently dying at 7 A.M. with faint respiration and the blood sugar was 10 mg. per 100 cc. He recovered after 20 cc. glucose solution (50 per cent) were given intravenously. Death occurred within a week from tuberculosis and amyloid disease.

[31] From Root and Bloor. Loc. cit., p. 563.

discovered simultaneously with the discovery of the diabetes in 1 case and at twenty-three years after the onset of the diabetes in 2 cases. The diabetes was mild in 5 of the 56 cases and the insulin requirement in 53 cases varied from 6 to 112 units a day. Weight loss had been considerable in the majority of patients

[illegible]

1946. Then x-ray evidence of recurrence required bed rest, and death occurred in August, 1946.

The results in the cases operated upon give reason to believe that this type of surgery performed in properly selected patients may afford another ray of hope for the diabetic patients who develop pulmonary tuberculosis

G CHEMOTHERAPY, DIET AND INSULIN

Specific Chemotherapy.—A large number of organic compounds are capable of inhibiting the growth of the tubercle bacillus *in vitro*, but few have been found with such activity *in vivo*. In recent years, several compounds effective *in vivo* have been discovered and have received thorough clinical trials. In 1944, streptomycin was discovered and its tuberculostatic influence in animals and humans was soon demonstrated. In 1946, the favorable effects of para-aminosalicylic acid (PAS) were announced. In 1952, the favorable effects of Isoniazide were reported. Because of the wide variations in the course of tuberculosis and the complexity of problems involved in new treatment, organized studies of hundreds of patients were necessary and carried out through the co-operation of many hospitals As a result of studies and clinical experience, it was found that resistance to individual drugs often developed in periods of 2 to 4 months The best results were obtained with the simultaneous use of two or even three drugs.

At the New England Deaconess Hospital, the use of these drugs has been an important part of the treatment of tuberculous patients, particularly before and after surgical treatment Many patients have been treated with moderate or even large doses without disturbance of the diabetes Streptomycin in doses up to 1 0 gm per day, sometimes with Dihydrostreptomycin, has been employed The toxic effects upon the vestibular apparatus, frequently reported when Streptomycin is given intramuscularly in doses of 2 0 gms daily, were not seen in any of the diabetic patients, since doses exceeding 1 0 gm a day have rarely been used and then only for short periods No toxic symptoms with Isoniazide were observed in any diabetic patients, although one non-diabetic patient developed a severe peripheral neuritis

[illegible]

in controlling the tuberculosis.

less than one year, and represented the terminal stage of chronic tuberculosis The earlier the diagnosis, the greater is the value of sanatorium treatment, and the more frequently can the advantages of collapse therapy and surgery be utilized

As a result of diminished insulin supplies in the British Zone of Berlin, Young[34] quotes medical opinion that, with increasing glycosuria and hyperglycemia, pulmonary tuberculosis running a rapidly fatal course had increased, as well as skin infections, perforating ulcer and gangrene.

TABLE 102 —DURATION OF DIABETES AND PULMONARY TUBERCULOSIS IN 456 FATAL CASES*

Period	*No of Cases*	*Diabetes, years*	*Tuberculosis, years*	*Total Diabetic Deaths*	*Per Cent Tuberculosis*
1898–1914	19	5 4	2 7	312	5 6
1914–1922	47	5 2	3 0	805	5 8
1922–1930	87	6 2	3 1	1278	6 8
1930–1938	128	9 9	3 3	1880	5 6
1938–1946	86	11 6	5 5	2734	2 5
1946–1950	45	10 3	3 2	2290	2.1
1950–1956	44	12 5	4 5	4183	1 5

* We are indebted for the tabulation of these data to Mr Herbert H Marks of the Statistical Bureau of the Metropolitan Life Insurance Company

The activation of a tuberculous pulmonary process through the use of cortisone or ACTH has been reported by King,[35] Popp,[36] and Fred.[37] Animal experimentation also indicates that tuberculous lesions may be disseminated more easily and more rapidly under the influence of cortisone trea[illegible]

O[illegible] ral years duration, developed a flor[illegible] subsided under treatment with ACT[illegible] one left this country and returned some months later with an active skin process X-ray examination in 1950 had shown a slight fibrosed lesion at one apex Post-mortem examination (June 1951) showed an active and extending area of pulmonary tuberculosis with cavitation.

In some way the resistance to tuberculosis is lowered during emaciation In obesity the trend of fat metabol[illegible] Fat tends to be stored up [illegible] the intermediaries of fat m[illegible] In diabetes with loss of weight, on the other hand, the fat metabolism is catabolic Beware of too rapid weight reduction in a diabetic.

J PREVENTION OF TUBERCULOSIS

Prevention of tuberculosis in diabetic patients must constantly be borne in mind Avoidance of contact with open cases must be brought about by

[34] Young Lancet, *1*, 125, 1949
[35] King *et al* Jour Amer Med Assn, *147*, 238, 1951.
[36] Popp *et al* Ibid, *147*, 241, 1951
[37] Fred *et al* Ibid, *147*, 242, 1951

H. COMA AND COMPLICATIONS IN TUBERCULOUS DIABETICS

Coma and tuberculosis frequently occur in the same patient contrary to the former belief that coma was rare in the tuberculous diabetic. More important is the fact that pulmonary tuberculosis often develops after *attacks of coma. Bertram*[22] *states that 80 per cent of his asthenic diabetics* developed tuberculosis after having diabetic coma. Grafe[23] cites a case of coma and tuberculosis requiring 2770 units of insulin.

Between 1923 and 1929 pulmonary tuberculosis developed in 8 per cent *of 105 diabetic patients within three years of recovery from coma.* Among 97 patients treated for coma between February, 1929, and November, 1932, 24 died of other causes within a year or two. Of the 73 patients remaining, 13 developed tuberculosis within five years. Among 804 instances of coma in 598 patients treated at the New England Deaconess Hospital, up to July 1, 1951, 128 have died since discharge, and of these 20 died of tuberculosis However, 66 of these 598 patients died between 1951 and 1958, with but a single death from tuberculosis. (See page 564).

The complications occurring in tuberculous diabetics are numerous, including gangrene, coronary arteriosclerosis and cirrhosis of the liver. Among the children with tuberculosis, cataracts, carbuncles, retinitis proliferans and coma have occurred

I PROGNOSIS OF TUBERCULOSIS IN DIABETES

The duration of life in diabetic patients with tuberculosis is sometimes surprising. The effect o
treated with insulin livec
5.4 years after the onset
1950, pulmonary tuberculosis had been present in 54 cases for more than five years, the average being eleven years. In fact, the prognosis for pulmonary tuberculosis in diabetics may be better than in non-diabetics, if they are discovered at the same stage of tuberculosis.

Nevertheless, the combination is to be dreaded, as shown by Table 102, which summarizes the du
cases Clearly the durati
The duration of life after
the average duration of diabetes before the onset of tuberculosis has also increased from 2.7 years in the period 1898–1914 to 8.0 years for patients dying with tuberculosis in the period 1950–1956.

Only by the earlier discovery of tuberculosis in an incipient stage can the *prognosis be greatly improved* In the aged, arteriosclerotic complications affect the course and shorten life Nevertheless, in 49 cases where the diabetes began after the age of sixty years, the average duration of life after the onset of the diabetes in 30 fatal cases was eight years The average *duration of life after discovery* of tuberculosis in this group, however, was

[22] Bertram P 76, loc cit, p 350
[23] Grafe Loc cit p 503

Chapter 24

CANCER AND DIABETES

ALEXANDER MARBLE, M.D.

A. INCIDENCE

THAT cancer is more common among diabetic than non-diabetic individuals has been the conclusion of most workers who have studied the problem. However, others have been skeptical as to any truly higher incidence of cancer among diabetic than non-diabetic individuals. Certain considerations on each side of this question will be presented in the discussion which follows.

Jacobson,[1] using data from death certificates and matched hospital reco- [illegible]

[illegible] ed that [illegible] Thus [illegible]

Ellinger and Landsman[2] found that in 1933 to 1941, of 1280 diabetic patients seen at Montefiore Hospital in New York City, 39, or 3.04 per cent, had malignant disease. The incidence of cancer was [illegible]

[illegible] of associated causes of death (as recorded on death certificates) in individuals dying with cancer in Massachusetts during a ten-year period, Wilson and Maher[3] observed that diabetes and cancer occurred together much more frequently than would be expected on the assumption that the two diseases are independent. They state that "it would appear that either diabetics tend to develop cancer or that cancer patients tend to develop symptoms recognized as diabetic."

In the series of Warren and LeCompte[4] comprising 818 diabetic patients on whom a post-mortem examination was done (made up largely of patients

1 Jacobson: Jour. Insur. Med., *3*, 51, 1948; Millbank Mem. Fund Quart., *26*, 90, 1948.
2 Ellinger and Landsman: New York State Jour. Med., *44*, 259, 1944.
3 Wilson and Maher: Am. Jour. Cancer, *16*, 227, 1932.
4 Warren and LeCompte: Loc. cit. p. 170.

the discovery and isolation of such cases in the families of diabetic patients. Good hygiene must include adequate rest, fresh air, outdoor life, regular exercise, and pasteurized milk. Summer camps should be utilized for diabetic children with calcified glands and positive skin tests Diabetic girls may become nurses. Early use of insulin and constant control of the diabetes are fundamental in maintaining nutrition and resistance This constituted a major reason for the establishment of the Hospital Teaching Clinic adjacent to the New England Deaconess Hospital where ambulatory patients can come to receive evaluation and instruction.

Detection of tuberculosis in diabetics will never be made at a reasonably early period until routine roentgenograms are taken at frequent intervals and always upon the slightest suspicion of pulmonary disease. Indeed, in hospital routine roentgen rays are more important than routine Wassermann tests.

Future.—Prevention of the excessive tuberculosis in young diabetics is *attainable by new methods of control. That diabetes and diabetic ketosis* lower resistance to tuberculosis especially in patients under forty years of age[39–40] needs no clinical proof. Today, experimental evidence suggests a possible reason why young diabetics who develop pulmonary tuberculosis also frequently develop retinitis proliferans and diabetic nephropathy. Cortisone and alloxan diabetes both appear to lower natural resistance[41–45] to invasive tuberculosis Both increase glycosuria and hyperglycemia In diabetic coma, increased urinary secretion of corticosteroids suggests that in ketosis,[46, 47] so frequent in young diabetics, repeated periods of increased cortisone production may occur with consequent impairment of resistance

coronary occlusion

[38] Root Loc cit, p 564
[39] Mahns Loc cit, p 570

1951

Cambridge,

If one considers the influence of the asserted tendency for two major

diabetic now approaches the normal individual more and more. His life expectancy at the time of development of diabetes is already more than half as great as that of the non-diabetic and his length of life is steadily increasing. Therefore, it seems logical to assume that at the present time this principle can be applied to diabetes to a less extent than to other major diseases.

The age at death of diabetics has increased from 46.7 years in 1914–1922 to +65 years in 1950–1955, thus bringing more patients into the cancer zone. Not only has the average age at death of individuals in the general population in Massachusetts increased (from 42.9 years in 1915 to 64.4

cancer in the sixth and seventh decades than in the fifth decade of life.

The discussion above indicates that it is difficult to draw conclusions regarding the relative incidence of cancer among diabetics and non-diabetics. Certain data, if considered by the usual statistical methods and standards, appear to indicate that cancer is more common in diabetes but, as pointed out above, there are serious objections to such a conclusion.

B. INCIDENCE OF DIABETES AMONG PERSONS WITH CANCER

and Rawson[8] at the Memorial Center for Cancer and Allied Diseases in

fever or those who had received recent steroid or nitrogen mustard therapy were excluded.

[6] Freund: Wien med Bl., *8*, 268, 1885.
[7] Glicksman, Myers and Rawson: Med Clin North Am., *40*, 887, 1956.
[8] Glicksman and Rawson: Cancer, *9*, 1127, 1956.

on the Joslin Clinic [illegible]
were 81 patien
regarding the
in Table 103.
has been a steady rise in the percentage of cancer deaths to total deaths from 8.7 in 1922–1926, to 10.3 in 1950–1955. In a relatively small series of 640 deaths in 1956–1957, the percentage had risen to 11.3; it remains to be seen whether this trend will be borne out by experience in the next few years

TABLE 103.—INCIDENCE OF CANCER AMONG DECEASED DIABETICS, 1898–1957[1,2]
(Experience of Joslin Clinic)

Period	*Deceased Diabetics*	*Cancer Deaths*	*Per Cent Cancer Deaths of all Deaths*
1898–1914	326	5	1.5
1914–1922	836	32	3.8
1922–1936	4138	362	8.7
1937–1943	3623	326	9.0
1944–1949	4116	400	9.7
1950–1955	4376	452	10.3
1956–1957	640	72	11.3

[1] Based on deaths reported through December 11, 1957.
[2] Table prepared with the assistance of the Statistical Bureau, Metropolitan Life Insurance Company

TABLE 104.—RATIO OF CANCER DEATHS TO TOTAL DEATHS IN MASSACHUSETTS[1]

Year	*Percentage of Deaths Due to Cancer*			
	All Ages	*40–49*	*50–59*	*60–69*
1895	3.49	7.54	10.32	8.87
1900	4.12	8.67	11.07	9.36
1905	4.94	9.42	11.87	10.59
1910	5.77	10.38	13.20	11.33
1915	6.92	11.17	14.39	13.15
1920	7.75	11.96	17.12	14.97
1925	10.10	14.04	17.83	16.74
1930	11.74	14.49	19.13	17.33
1935	12.79	15.44	18.46	17.71
1940	14.26	17.70	19.95	18.38
1945	15.25	17.91	20.57	19.57
1950	17.63	22.54	21.29	21.77
1955	17.75	26.14	26.70	22.52

Up to the present, as is evident from Table 104, the ratio of cancer deaths

[1] Compiled from Table 102 of Bigelow and Lombard Cancer and Other Chronic Diseases in Massachusetts, Boston, Houghton, Mifflin Company, 1933. Figures for 1930 through 1955 are available through the courtesy of Dr Herbert L Lombard

7 5 years for the duration of diabetes, as stated above, it was apparent that in most instances the onset of diabetes came well before that of cancer. Furthermore, of the 185 cases, in 159 the onset of diabetes preceded that of cancer symptoms, and in only 26 instances did the onset of cancer symptoms precede those of diabetes In other words, one was dealing with a group of diabetic patients who later developed cancer, rather than with a group of patients with malignant disease who developed diabetes. The figure of 2 5 years, for duration of cancer symptoms from onset until death, is slightly greater than that of approximately two years found by Macdonald[11] in a study of cancer deaths in Massachusetts in 1932.

Among the total group of 243 fatal cases in the authors' series, the ten most common sites of cancer were as follows. breast 35 cases, pancreas 33, uterus 27, stomach 17, urinary bladder 15, liver 14, large intestine (exclusive of

could l

metast

individuals

2. SERIES STUDIED IN 1940 AND 1952.—In 1940, and again in 1952, we studied the records of 101 diabetic patients with cancer treated at the Joslin Clinic in the five-year period from 1934 to 1938, inclusive Of these, 34 were male and 67 female In the 1952 follow-up study it was found that up to January, 1952, 96 of the 101 patients had died Analysis of the data yielded findings which were in essential agreement with those in the larger series of 256 cases

3. SERIES STUDIED IN 1958 —The most recent study on this subject[11a] utilized a modified life table methodology for patients first diagnosed as having diabetes 1937 to 1941 Sixty-seven cases were observed while the expected number was 74 3 This seems reasonably satisfactory proof that individuals with diabetes do not show greater incidence of cancer than the general population of the same age and sex distribution

D CANCER OF THE PANCREAS

Incidence.—Cancer of the pancreas deserves special mention Both in the series of 256 cases of cancer reported upon in 1934, and in the series of 101 cases studied in 1940 and 1952, carcinoma of the pancreas comprised a relatively high portion of the total, forming 13 per cent of the former and 12 per cent of the latter series

The above fig

[11] Macdonald Am Jour Pub Health, *28*, 818, 1938
[11a] Joslin, Lombard, Burrows and Manning Submitted for publication
[12] Hoffman San Francisco Cancer Survey, Third Preliminary Report, Newark, N J, The Prudential Press, p 29, 1925
[13] Hoffman New England Jour Med, *211*, 165, 1925
[14] Bigelow and Lombard, P 264, Loc cit, p 416.

The results of the study by the Memorial Center ... striking. F... in 36.7 per c... with only 9. ... lesions pro... from the st... per cent of the control group and 13 per cent of the cancer group.

Considering only those sites of cancer in which ...

incidence of 64 ... epidermoid carci... per cent incidence of positive responses. There were only 5 cases of cancer of the pancreas but 4 of these had positive tests

The papers of Glicksman, Myers and Rawson and of Glicksman and Rawson should be consulted for an extensive bibliography ...

... significantly slower in individuals with cancer than in control subjects Glicksman and Rawson speculate as to the mechanism involved which, at the present time ... consistently greater ... endocrine tumors or ... suggests that a study ... may prove fruitful

C CASES OF CANCER AND DIABETES IN AUTHORS' SERIES

1 SERIES STUDIED IN 1933.—In 1933 a study was made[10] of the records of approximately 10,000 ...

... occurred ...

... cancer symptoms up to death and in this group the average was 2 5 years Allowing for inaccuracies, this figure was still so much less than that of

[9] Marks and Bishop Proceed Am Assn Cancer Research, 2, 131, 1956
[10] Marble New England Jour Med, 211, 339, 1934

tioned earlier, Glickman and Rawson[19] found that 4 of 5 patients with cancer of the pancreas gave abnormal findings in glucose tolerance tests

Carcinoma of the pancreas probably does not cause overt diabetes oftener because: (1) the tumor is usually situated chiefly in the head and body of the gland, whereas most of the islet-bearing tissue is in the tail of the organ (2) Islet tissue seems capable of repelling invasion possibly because of its independent blood supply.

[19] Glickman and Rawson Loc cit p 579

Company[15] there were 4840 deaths, or 4.2 per cent, from cancer of the pancreas. In the United States during the same period there were 1,143,231 deaths reported as due to malignant disease; 51,161, or 4.5 per cent, were due to cancer of the pancreas.

Among our own cases, the patients with cancer of the pancreas numbered 33 in the first series and 12 in the second series, a total of 44 cases (Case 11647 was included in both series). Of these, 18 were males and 26 were females. At the age at which cancer of the pancreas is most common, there are about twice as many females as males with diabetes, so that actually the sex incidence was higher in males than is apparent at first glance. In the literature the condition has been reported to occur almost twice as often in men as in women, although in Kiefer's[16] series there was almost equal distribution between the sexes. *In our 44 cases the average duration* of diabetes at death was 3.6 years, as opposed to an average duration of cancer symptoms of 1.0 year. The average age at death was 62.2 years. In practically all cases the tumor occupied the head of the organ.

abdomen.

The Relationship Between Cancer of the Pancreas and Diabetes.— The interesting question naturally arises as to whether in these cases diabetes may have arisen because of the involvement of the pancreas by the carcinomatous growth. The impairment of pancreatic function both as regards internal and external secretion by the encroachment of tumor tissue certainly affords an explanation for the occurrence of diabetes far more satisfying than one is accustomed to find. Although in the present series the fact that the onset of diabetes preceded by an average of 2.6 years the onset of symptoms referable to the pancreatic tumor is against such a conclusion, it must be admitted that the duration of diabetes among the cases of cancer of the pancreas, 3.6 years, is the shortest duration among any group of diabetics under observation. An opinion frequently expressed is that although glycosuria is not infrequent in cases of carcinoma of the pancreas, actual diabetes seldom occurs. It is possible, however, that al-

develops more frequently than is generally supposed." As has been men-

available, this group of patients has a much better chance of survival and cure than ever before

Table 105 summarizes the operative experience on diabetic patients at the New England Deaconess Hospital from 1923 through 1956 It will be seen that from 1942 on, coincident with the advent of the antibiotics and possibly coincident with better anesthesia, the mortality dropped and has remained essentially unchanged.

B. VARIETY OF OPERATIONS

With the passage of time, the number of major amputations in relation to local procedures on the foot has dropped—largely due to the use of antibiotics and the development of the transmetatarsal amputation to be discussed later Surgery for carbuncles and other abscesses has dramatically declined Much of the latter surgery is preventable if the patient is properly educated by his physician Since more than one-third of all the surgical deaths follow amputation, the problem of preventing lesions

arteries, nose, throat, *etc* It does not include dental operations.

TABLE 106 —CAUSES OF DEATH IN 69 SURGICAL DIABETICS
From January 1, 1951 to January 1, 1957

Arteriosclerotic heart disease (coronary thrombosis)	
Following amputation	20*
Post abdominal or chest surgery	14
Carcinoma (incurable at operation)	14
Gastro-intestinal hemorrhages—shock	3
Cerebrovascular accident	3*
Uremia	2
Pulmonary embolism	2*
Septicemia	2
Peritonitis	2
Liver failure	2
Pancreatitis	1
Pneumonia	1
Miscellaneous	3

* Surgery for gangrene of foot

C PROGNOSIS OF THE SURGICAL DIABETIC

The prognosis for the surgical diabetic has steadily improved. The mortality for our surgical cases at the New England Deaconess Hospital

Chapter 25

SURGERY AND DIABETES

Frank C. Wheelock, Jr., M.D. and Howard F. Root, M.D

A. INTRODUCTION

Surgery in patients with diabetes presents all the facinating problems of surgery in general with additional ones peculiar to diabetes and its complications. The long-lived diabetic patient may have any known surgical disease, but he may respond to it differently with respect to symptoms produced by the surgical disease or by his own reaction to infection. Frequently there is *impaired sensation or diminished blood supply to a part* (notably the lower extremity) which may create complicated situations. Therefore, decision both as to diagnosis and treatment may be more difficult than in the non-diabetic.

Aside from the surgical problems, a serious metabolic disease must be controlled at all times and not infrequently in addition cardiac, renal or cerebrovascular complications of significant proportions will require consideration and treatment.

Table 105.—9630 Diabetic Operations
(Jan. 1, 1923 to Jan. 1, 1957)
New England Deaconess Hospital

	1923–1941	*1942–1945*	*1946–1949*	*1950–1953*	*1954–1956*
Amputations, Major	733	269	216	320	203
Amputations Toes, Fingers	450	322	417	223	211
Carbuncles	116	18	9	12	
Ulcers, Abscesses	431	108	115	34	12
Thyroid	213	66	61	51	43
Tonsillectomy	186	48	36	18	10
Laparotomy	429	132	286	245	237
Genito-urinary	151	46	88	75	104
Pelvic-rectal	234	56	167	78	30
Ocular	148	49	83	65	47
Chest				44	28
Miscellaneous	431	339	386	356	314
	3,551	1,453	1,864	1,523	1,239
Fatal	*260*	*32*	*37*	*34*	*42*
Per Cent Fatal	7.3	2.2	1.9	2.2	3.3

more difficult for the postoperative patient to take liquids or food freely, besides possibly releasing latent acid bodies whose excretion would irritate the kidneys Coma can be avoided by the administration of a diet of 100 grams or more of carbohydrate with the simultaneous use in three- to eight-hour intervals of insulin sufficient to enable the patient to utilize it. Invariably in the twenty-four hours subsequent to operation the patient receives 150 grams carbohydrate by mouth, subcutaneously or intravenously.

The danger of a clean wound in a diabetic becoming infected is slight if the diabetes is properly controlled Given an infection, it is freely granted that the disease becomes worse, prevent the infection, and healing is prompt. In so close a relation do both stand to each other that a loss of tolerance for carbohydrate may be recorded on the diabetic chart before the wound discloses a retrograde course. The presence of an excess of sugar in the blood may not be so serious as acidosis, but neither is desirable. The skin, [illegible]

and so favors hyperglycemia and acidosis Control this infection and then [illegible]

kidneys among the diabetics is to be blamed for the serious prognosis equally with the diabetes [illegible]

[illegible] liver storm after a simple cholecystectomy The explanation seemed clear when chemical analyses of an excised portion of the liver showed at the end of the operation almost no glycogen present and a great increase in fatty acid

In diabetic patients the occurrence of shock, whether as a result of surgical operation or severe medical disease such as coronary occlusion, often [illegible]

carried out by Haist and collaborators,[3,4] as well as by other students In

[2] Coller and Jackson Jour Am Med Assn, 112, 128, 1939.
[3] Haist and Hamilton Jour Phys, 102, 471, 1944
[4] Haist New York Diabetes Association, 1946.

for 1923 to 1926, was 11.5 per cent, while from 1923 to 1941, it was 7.3 per cent. The lowest mortality was reached in 1949, when it was 1.9 per cent. Fro [illegible]

C [illegible]

sep [illegible]

congestive failure or with myocardial infarction takes first place and is most frequent following surgery for gangrene of the lower extremity. This might be anticipated since arteriosclerosis is not usually a local disease and commonly affects the coronary arteries and the peripheral arteries simultaneously. The mortality for surgery indicated for gangrene in this period is 3.1 per cent.*

The patients liste [illegible] post-operatively of [illegible] The other items list [illegible] tion is not common but does occur.

An important factor in determining prognosis for the surgical diabetic [illegible]

[illegible] to the patient demands that he be treated in the medical wards where he can obtain the detailed and intimate treatment which the severest medical diabetics receive. A surgeon unfamiliar with insulin should not undertake alone the care of a diabetic. Cases of diabetes in coma are visited by a physician every hour, surgical cases need almost as much medical care. For [illegible] cases [illegible] in ev [illegible] As a [illegible] immediate in that preventive measures have not been instilled early enough into the minds of the patients

Concentration of the surgical treatment in the hands of a single team is wise "Better a youngster who has had special experience with the care of diabetics than the senior surgeon who includes diabetes with a hundred other interests"[1]

Factors Favoring Success —Among the elements formerly hindering success, acidosis and a liability to infection are now largely eliminated Coma has become only an accident *Old time surgery courted it* (1) by the administration of chloroform and ether, only too frequently by untrained hands, (2) by the sudden restriction of carbohydrate prior to the operation with the desire to lower the glycosuria, (3) by the attempt to relieve the patient's hunger thus caused with an excess of protein and fat, wholly unmindful that in so doing acidosis was favored; (4) by the large doses of sodium bicarbonate which upset the digestion, making it still

* 25 deaths in 812 toe, transmetatarsal or leg amputations

[1] Professor E D Churchill Personal Communication

Evaluation of Operative Risk.—In general it is important to remember that age for age the diabetic patient is older physiologically than the non-

D. DIET IN DIABETIC SURGERY

Malnutrition in diabetic surgical patients has long been recognized, but

partial or moderate state of starvation Hypoproteinemia with its harmful effects upon wound healing and subclinical vitamin deficiency more and more concern the surgeon, especially in gastro-intestinal surgery.

Vitamins.—The use of vitamins for a few days prior to operation is

treatment must necessarily be continued after operation If the patient

grams

Protein.—One of the most serious dietary deficiencies in surgical patients is deficiency of protein Protein provides the necessary amino acids from which damaged tissue may be repaired as well as the amino acids necessary for the formation of hormones, antibodies, and enzymes Protein is important also both in carbohydrate and fat metabolism The usual measurement of protein stored in the body in the sick patient is the serum protein level This measurement is open to difficulties in interpretation since in an acute phase such as bad burns or hemorrhage, or intestinal obstruction, it does not give an accurate picture of the stores of protein In chronic disease a low serum level may indicate the loss of less important proteins in order to maintain more vital organs There can be no doubt that a low level of protein in the blood interferes with proper healing, as has been shown experimentally and clinically The low level of serum protein affects the osmotic pressure of the blood and causes edema. Actually a considerable degree of edema may exist before it is evident. Edema

shock caused in animals by anoxia of the extremities produced by tourni-

due in some way to changes occurring in the damaged and anoxic tissue of the animal.

clock strikes the hour Show him how to protect his lungs by long breaths and by turning over in bed In short, keep him busy getting well. A

reduced is forgotten, simply because the laboratory reports a positive diacetic acid reaction or a trace of sugar in the urine Be careful! Do not treat the laboratory test instead of the patient!

The factors which favor surgical success in diabetes are first of all an early

tion in hand, and the convalescence from the surgical complication utilized *to free the patient from sugar and acidosis The patient should be treated*

secure a sugar-free urine and a normal blood sugar before operation. Yet even in these cases if they are arteriosclerotic and of long duration one must be cautious not to lower the blood sugar rapidly or as low as in the younger diabetics

The *second factor* which favors success in diabetic surgery is the *adjustment of the diet to the surgical requirements* If there is no need for haste, any of the well-recognized systems recommended to get the patient free from

operating.

patient, and in other patients where concentrated protein and vitamins are desired

High Protein Tomato Soup	*Carbo-hydrate*	*Protein*	*Fat*	
Butter, 35 grams	0	0	28	
Casein, 15 grams	0	13	0	
Wheat germ, 15 grams	7	6	0	
Soy bean flour, 10 grams	5	5	2	
Milk, 240 cc	12	8	10	
Tomato purée, 2 tablesp	3	2	0	
Salt to flavor	—	—	—	
Total	27	34	40	Cal —604

Melt butter in top of double boiler Stir in casein, wheat germ, soy bean flour Mix in tomato purée and bouillon (other flavorings for variety) Add milk gradually, cook ten minutes

Salt and Water Balance.—Water balance for the maintenance of the body fluid

ticularly ea

acidosis or

However, without serious acidosis, the polyuria of uncontrolled diabetes may produce more than a slight degree of dehydration and also a disturbance in the salt metabolism Normal water intake by mouth varies from

and vaporization amounts to between 1000 and 1500 cc daily When diabetic patients were compared with hyperthyroid patients by Benedict and Root[7] at the New England Deaconess Hospital, the amount of insensible perspiration was found to vary from an extremely low value, or 15 grams per hour, in a child with dehydration and acidosis to 100 grams per

solved solid matter in twenty-four hours, and with a normal person the

centrating power of the kidneys and may rise to a level of 1439 cc when the specific gravity of the urine varies between 1 010 and 1 014 Under ordinary circumstances, therefore, the normal intake of water should vary from 2000 to 3000 cc in twenty-four hours, and the surgical patient with normal kidneys should have at least 2000 and preferably 3000 cc of fluid daily If renal function is impaired, then alterations in this amount may be necessary Actually, Ravdin[9] calculated that in seriously ill patients

[7] Benedict and Root Arch Int Med , 38, 1, 1926
[8] Lashmet and Newburgh Jour Clin Invest , 11, 1003, 1932
[9] Ravdin and Zintel P 847, loc cit , p 590

is not usually apparent until the weight of the affected part is increased by fully 10 per cent.

The treatment of hypoproteinemia in acute emergencies, such as is caused by severe burns, intestinal obstruction, *etc.*, usually requires prompt administration of blood plasma. When the loss has been that of whole blood, *as in frank hemorrhage and crash injuries, then whole blood should ge given* until blood volume is restored. For extensive burns Ravdin and Zintel[5] recommend the method of Evans: The body weight in kilograms times the percentage of body surface burned equals the amount of blood or plasma to be administered. Thus a 70-kg. man with a 40 per cent burn would receive 2800 cc. of whole blood or plasma in the first 24 hours, plus an equal amount of physiologic saline (2800 cc) and basic requirements of 5 per cent glucose and water.[5]

Chronic protein deficiency is usually considered a dietary problem, but frequently the possibility of administering sufficient protein by mouth to control a severe deficiency is remote. As preparation for surgery, whole blood transfusion may be indicated. If a 70-kg. man requires a restoration of 2 grams per cent in his serum albumin, that is from an observed value of 2 6 grams to a normal of 4 6 grams, he will need 60 grams serum albumin and thirty times that amount to restore the deficiencies of the rest of the body.[5]

The difficulty in administering so much protein is well illustrated in Case 27821, age fifty-seven years, who entered the New England Deaconess Hospital on July 19, 1945 with a large appendix abscess, which was operated on by Dr C. C Lund. Diabetes of seven years' duration had never been [illegible] per cent sugar and

coccus aureus resulted in sloughing the entire abdominal skin and subcutaneous tissue from the pubes to the ensiform and from flank to flank A continuous loss of protein from this area occurred during the period from late July until September. The patient was a large woman, her usual weight being 200 pounds. The plasma protein value varied from 3.8 to 4 8 grams per cent. In addition to repeated transfusions she received on certain days, 4000 cc. of 5 per cent amigen solution in glucose during the period when she could take nothing by mouth About September 10, the infection having been controlled, her appetite returned and she was given *protein by mouth in amounts planned to provide 250 grams* consisting of steaks and other forms of meat, cheese, eggs, milk and aminoids Actually her protein intake by mouth during this period exceeded 200 grams in a day on only four days However, she took from 175 to 200 grams of protein daily for thirteen days She was finally discharged on October 20, having made complete recovery. The best proteins for restoring protein deficiency are meat, milk, eggs, wheat, and soy beans. A recipe first suggested by Stare and Thorn[6] provides a tomato soup which was used with this

[5] Ravdin and Zintel In, Wohl and Goodhart, Modern Nutrition, Philadelphia, Lea & Febiger, p 846, 1955

[6] Stare and Thorn Jour Am Med Assn, *127*, 1120, 1945

familiar sight in any hospital, but it is also wise to supply him liberally with liquids the day before These should include broths on account of the salts therein contained, coffee, tea, water, and if necessary, salt solution or tap water by rectum. It is a safe, routine procedure to inject salt solution subcutaneously
is this desirable
urine, nitrogen
the excretion of acetone bodies There are few diabetics who do not need an intravenous or subcutaneous injection of salt solution at the time of an operation

units of insulin a day and later, after a period of six months, was in good equilibrium with only 100 units of insulin a day. The failure of the respiratory

removed from the blood stream In their normal case the respiratory quotient rose from 0 77 to 0 81.

The levels of circulating eosinophils as a measure of adrenal cortical response
diabeti
ished
second
preope
mally to the initial stress of surgery but its reserve capacity was insufficient to maintain the eosinopenia for 48 hours (See page 126)

The importance of correcting any anemia that exists is great Not a few

[11] Coller, Campbell, Vaughan, Iob and Moyer Ann Surg , *119*, 533, 1944
[12] Pijoan and Gibson Am Jour Physiol , *121*, 534, 1938
[13] Field and Marble Proc Soc Exp Biology and Medicine, *77*, 195, 1951

with drainage, the following figures would apply: For vaporization, 2000 cc.; for urine, 1500 cc.; bile drainage, 1000 cc., Wangensteen drainage, 3000 cc.; total 7500 cc. fluid required. Actually, in diabetic patients, 7000 cc of fluid is not an excessive amount to give provided acidosis has pro-

[illegible]

gen solution in glucose and 1000 cc. of 5 per cent glucose in salt solution

[illegible]

successfully. In her case also the high protein tomato soup proved acceptable in the diet.

When salt intake is greatly reduced or when there has been a great loss of salt by vomiting, then the kidneys conserve salt and the concentration of salt in the urine is greatly reduced Thus, in diabetic coma when there has been a great loss of salt by vomiting or in the urine preceding coma, it will be found that the gastric content contains no free hydrochloric acid and the chloride content of the urine is low When chloride is lost as in vomiting, the kidneys retain this element and excrete sodium When basic elements are lost as in diarrhea, sodium is retained and the chloride is excreted In surgical cases water and salt must be kept constantly in mind. In patients with high fever or hyperthyroidism additional amounts of fluid are lost steadily Losses of fluid when continuous gastric drainage is carried out may be considerable. Dehydration may be evident clinically by the pinched expression, dry skin and tongue, increased thirst and low urinary output Coller and Maddock[10] consider that when these findings are present dehydration is equivalent to at least 6 per cent of the body weight and the patient, therefore, should be given fluid equivalent to this amount in addition to the normal daily requirement However, it must be pointed out that in elderly patients with cardiac complications caution should be observed Actually in diabetic patients dehydration may often be much more severe, and following diabetic coma we have not infrequently given in the course of twenty-four hours 10, or even up to 15 per cent of a patient's body weight without the production of edema

When hypochloremia is present, dullness, lethargy, muscular twitching, acidosis or alkalosis are commonly observed Every patient about to be operated upon for a serious abdominal condition should have a determination of the plasma chloride The amount of sodium chloride required to raise the serum chloride one milliequivalent per liter is 13.3 milligrams of sodium chloride per pound of body weight During postoperative treatment, determinations of plasma chloride levels have proven the best means of following the condition of patients requiring intravenous feeding.

[10] Coller and Maddock Surg Gynec and Obst [illegible]

woman aged sixty years was admitted with renal sepsis The urine was negative for sugar and after operation she developed diabetic acidosis. The diabetic condition was not known before operation due to renal insufficiency, which caused an absence of glycosuria despite a high blood sugar.

E. INSULIN IN DIABETIC SURGERY

An early position on the surgeon's operating list is desirable in order to avoid hypoglycemia from the continuing action of protamine insulin. If ✓ insulin has been used regularly by the patient, give the same total number of units in twenty-four hours, at the time of operation, but divide into smaller and more frequent doses, irrespective of meals On the morning of

contain sugar and omit it when two successive specimens are sugar-free Avoid worry by giving small doses every three or four hours, more rarely six to eight hours, rather than larger doses infrequently, until acquainted with the tolerance of the patient During convalescence when the urine is sugar-free, often test the need for insulin by omitting or reducing a single dose, usually the noon dose first, then the evening dose It is as important to have a blood-sugar test in the late forenoon as before breakfast for a guide to insulin administration

Although many older surgical diabetics are relatively insensitive to

excessive

metabolism are necessary to produce the resistance found in diabetic patients with infection

Allergy to insulin is sometimes associated with acute infection The occurrence of generalized urticarial reactions following the administration

ears at onset of diabetes in January
She gave it up subsequently and
when she developed an infection
ecause of glycosuria and rapidly

[a] Hayward and Duncan Am Jour Med Sci, 198, 396, 1939

diabetics develop low hemoglobin values without actual blood loss—particularly the group who have neuropathy and nephropathy with high urinary losses of albumin. If we expect patients to heal surgical incisions or to overcome infections, an adequate hemoglobin level must be attained. Frequently prolonged failure to heal a large defect has yielded surprisingly to repeated transfusions. A low hemoglobin level must never be disregarded.

Diet for Surgical Diabetic Patients Before and After Operation.—If the case may be prepared for operation in a leisurely manner, no special change need be made in the regular program to free the urine from sugar and acid, save that the food should be prepared in simpler form. Coarse diabetic foods should be omitted. If the situation is acute, and but a day or a few hours are available, sudden restriction of carbohydrate, particularly when dealing with severe diabetics or elderly patients, must be avoided, and great care taken not to upset the stomach. The simplest foods are, therefore, the best. Except when the nature of the operation requires special dietary regulations, liquids, such as oatmeal gruel made *with water, hot tea or coffee (with crackers or toast) are given freely, and* ginger ale and orange juice with egg white are given sparingly on the day after operation On the second postoperative day milk and, if the patient desires, cooked cereals, junket or boiled custard are added to the diet. Thereafter the diet is increased according to the patient's tolerance and desires. If possible, 100 to 150 grams of carbohydrate are given daily, any amount not taken by mouth being supplied by parenteral administration in the form of 5 per cent dextrose by vein or 2 5 per cent dextrose in physiological solution of sodium chloride under the skin. Occasionally as much as 300 grams of carbohydrate may be given in cases of severe damage to

will become sugar-free before recovery from surgical lesions. In fact, a surgical operation is ofttimes a blessing rather than a curse.

The *diet after operation* should certainly contain as a minimum between 0 66 and 1 25 gram of protein per kilogram body weight, and a daily intake up to 125 grams has been used in severe infections, especially of the feet. *When dealing with infections, an overrigorous attempt should not be made to get the patient sugar-free either before or after operation* With surgical treatment to remove or drain the infection, the tolerance for carbohydrate will improve It is painful to look over the protocols of cases suffering from infections in years gone by, who were terribly undernourished with the purpose to make them sugar-free

The advantage of a routine blood-sugar determination in preparation of a diabetic patient for surgery is illustrated by one case in the excellent summary of 80 diabetic operations by Rabinovitz and Weisman [15] A

[14] McKittrick and Root Arch Surg, *40*, 1057, 1940
[15] Rabinovitz and Weisman New England Jour. Med, *219*, 423, 1938

(c) *Cyclopropane* This anesthetic agent, if care is taken to prevent explosion, is satisfactory. Patients with irritable hearts may develop cardiac arhythmias

(d) *Spinal Anesthesia* In operations on the extremities this method has been satisfactory. The dosage of pontocain required has little toxicity. There have been no unfavorable effects at the New England Deaconess Hospital In lower abdominal surgery it is also satisfactory. We have

the spinal cord.

(e) *Novocaine.* Local anesthesia frequently works admirably and often shortens the period for employment of one of the group of anesthetics previously discussed *In a region where the blood supply is good, one need* not hesitate in clean cases to use novocaine

(f) *Pentothal With or Without Curare.* Pentothal by itself does not produce muscle relaxation However, for many minor procedures relaxation is not necessary and pentothal serves admirably. If relaxation is essential, the addition of an agent which paralyzes skeletal muscle such as curare or enectine is possible Our experience with this combination of agents is limited but so far quite satisfactory. In the critically ill patient who has had a hemorrhage, relaxants can be dangerous

With all *these agents it is important to remember that much depends on* the experience of the anesthetist with a given drug The choice of agent usually should be left to him

G CARBUNCLES

the cause of septi-
yet such was the
antibiotics avoids
that not
cillin, if
must be
can be

determined by sensitivity tests in the bacteriologic laboratory

This maneuver was helpful in Case 35918, an 18-year-old girl, who entered the hospital in coma with a large carbuncle of the chin No improvement was obtained with penicillin in the first few days Sensitivity tests showed aureomycin to be the drug of choice and the response to this was rapid

Carbuncles like coma and gangrene are more apt to appear in the fat than in the thin diabetic Scrupulous cleanliness is essential in order to avoid them "The washed neck, like the watched pot, never boils," (Brigham)

The diabetic condition is not extremely severe in many patients when

be reduced rapidly to avoid hypoglycemia.

extending infection. Generalized urticarial reactions occurred with three different types of insulin and she entered the New England Deaconess Hospital with gangrene of the foot, fever and acidosis in spite of the fact that she had received 120 units of insulin the day before. She required 250 units of insulin a day to control the acidosis in spite of the severe urticaria. Almost immediately following the amputation of the infected leg diacetic acid disappeared from the urine and the urticarial reactions ceased A [illegible] transfer method Her case was reported by Root[17]

Protamine zinc insulin has been used at the New England Deaconess Hospital, but NPH insulin singly or with regular insulin is the usual choice at present. Lente insulin and Globin insulin are less frequently employed

F. ANESTHESIA IN DIABETIC SURGERY

The *anesthetic*, including its method of administration, contributes to the [illegible] ...h the aid of [illegible] one should [illegible] ...owledge so painfully acquired before the discovery of insulin. Every effort should be made to shorten the period of anesthesia, irrespective of the type of anesthetic used Avoidance of apprehension and excitement on the part of the patient is important It is valuable to have an anesthetist accustomed to diabetics

Preoperative medication should be kept at a minimum More than once a newcomer to the anesthesia department has ordered regular doses of narcotics or analgesics preoperatively with the result that the patient has come to surgery so depressed that operation was deferred to another day Actually in no patient is there reason to use narcotics preoperatively unless the lesion to be treated is painful. In the older diabetic, therefore, we use only atropine, and in the younger a modest to small dose of a suitable barbiturate, plus atropine

This policy avoids the anoxia shown by McClure, Hartman, Schnedorf and Schelling[18] to be produced by morphia and barbiturates given preoperatively

In general the choice of anesthetic so far as its effects on diabetic metabolism are concerned should be (1) local, (2) spinal, (3) general

(a) *Ether* During etherization the formation of glycogen is greatly reduced Ether anesthesia is a burden which a light case of diabetes may easily bear but which may change a moderate to a severe case, and to a severe case may prove fatal, yet with the help of insulin the harmful effects may be averted

(b) *Nitrous Oxide-oxygen* This combination is used only for inductions and is dangerous for long operations Relaxation of muscles is poor and anoxia a constant danger

[17] Root Jour Am Med Assn, *131*, 882, 1946
[18] McClure, Hartman, Schnedorf and Schelling Ann Surg, *110*, 835, 1939

Biliary Tract Disease.—The treatment of symptomatic gallstones is no different in the diabetic than in the non-diabetic The decision which is sometimes difficult to make is whether or not to remove asymptomatic gallstones The reasons for advising removal of these are, first, fear that later acute cholecystitis with the danger of abscess formation or perforation may occur, and second, that stones may lodge in the common duct These events might not happen for a number of years, but by that time the patient, who was a good operative risk when the stones were originally found, may have developed severe cardiac, renal, or central nervous system disease which could make surgery extremely hazardous

[illegible]

the mortality of operation is less than the future development of cancer of the gall bladder when cholelithiasis is present.

It would, therefore, seem reasonable to advise the removal of the diseased gall bladder in patients whose general condition makes the risk of surgery reasonable Each such case must be decided on an individual basis with more regard for physiological than chronological age The mortality at the New England Deaconess Hospital for uncomplicated cholecystectomy from January 1, 1947 to January 1, 1956, was in 198 cases only 1 per cent.

Pain in Diabetic Coma.—Patients not infrequently enter with diabetic coma and abdominal pain This can create a difficult diagnostic problem since an acute surgical abdomen could precipitate acidosis or coma, just as the latter can produce abdominal pain. With acidosis and coma the white blood count may reach very high levels indeed, so this is not a helpful test Also, with acidosis there may be marked rigidity of the abdomen and generalized tenderness The solution can usually be satisfactorily reached by carefully evaluating the history taken from the patient and his family to determine what the first symptoms were, and by repeated, careful

[illegible]

decision can almost always be made As in the case of all these patients, close teamwork between physician and surgeon is essential

General Considerations.—The diabetic patient facing surgery, particularly major surgery on the gastro-intestinal tract, which will prevent an adequate oral intake for a few days, deserves careful evaluation, particularly if the surgical problem has prevented eating for a few days with resultant lowering of the glycogen stores At such times, if conditions are improving so that the patient can eat, one might delay surgery for a few days If conditions do not indicate improvement, aggressive surgical interference is in order Since diabetics tolerate infections poorly, early surgery is best if the infected area can be drained or the offending organ removed

1. GANGRENE: ARTERIAL INSUFFICIENCY

Incidence.—Gangrene, dependent upon the diabetic predisposition to arteriosclerosis obliterans, has long been a dreaded and frequent complica-

All diabetics should be warned against becoming infected from others in the household. The husband of Case 1245 had boils; his wife contracted a carbuncle. The length of one of the crucial incisions in her back was 10 inches, yet she recovered.

II. SURGICAL DISEASES OF THE GASTRO-INTESTINAL TRACT

The surgical problems in diabetics are as a rule similar to those in non-diabetics. Thoracic, orthopedic and urological problems follow this rule for the most part. Cancer occurs in the usual locations but with greater frequency. Tuberculosis is slightly more common in the diabetic than in the non-diabetic.

The most difficult decisions surgically, aside from peripheral vascular problems, deal with the gastro-intestinal tract.

Appendicitis.—In diabetic patients this common disease may present a problem in diagnosis of seri[illegible]
and coma may be confused [illegible]
surgical diseases, to be discu[illegible]
is the relatively quiet, almost asymptomatic appendicitis case. Three examples of this come to mind.

[illegible]

TABLE 107 —AGE AT ONSET OF GANGRENE IN 1045 PATIENTS WITH SURGERY

Age at Onset Gangrene	1898–1922		1923–1939		July 1, 1939–Jan 1, 1946		Jan 1, 1946–Jan 1, 1951		Total	
	No of Cases	*Average Age at Onset*	*No of Cases*	*Average Age at Onset*	*No of Cases*	*Average Age at Onset*	*No of Cases*	*Average Age at Onset*	*No of Cases*	*Average Age at Onset*
30–49	8	44	19	46	6	49	12	44	45	46
50–59	28	56	99	56	43	55	67	55	237	56
60–69	40	65	217	65	76	65	125	65	458	65
70–79	8	72	120	73	61	73	83	73	272	73
80–	0	0	6	84	19	83	8	82	33	83
TOTALS	84	61	461	64	205	64	295	64	1045	64

tion. It accounts for approximately one-third of the diabetic patients in the New England Deaconess Hospital during the cold months and one-fifth of them in the warmer.

In recent years two surveys have emphasized the magnitude of the problem. The Committee on Diabetes of the Massachusetts Medical Society[19] studied the frequency and cost, both financial and in terms of *future disability, resulting from surgical lesions of the feet in diabetics in* 9 Massachusetts Hospitals. During the 12-month period, 502 patients spent an average of 26 days in hospital. Thirty-three deaths occurred among 332 operations. Arterial insufficiency was the underlying cause in 48 per cent of the patients. The financial cost, including hospital charges, but without any allowance for professional services for physicians or surgeons was estimated at $500,000.

In a survey of 3788 diabetics at King's College Hospital, London, Oakley, Catterall and Martin[20] found peripheral occlusive arterial disease absent *under the age of 40 years but increasing in frequency with each additional* decade reaching 23 per cent for those over 70 years of age. A report of fifty below-knee amputations is given. They noted the frequent association of ischaemia, neuropathy and sepsis

Analysis of the postmortem records of 28,240 males and 15,119 females over 10 years of age by Bell[21] brings out the remarkable effect of diabetes in intensifying and accelerating gangrene. Arteriosclerotic gangrene occurred in 0.66 per cent of non-diabetic males, but in 24.9 per cent in 466 diabetic males. Similarly for women, gangrene was present in 0.59 per cent non-diabetic females but occurred in *23.8 per cent of 499 diabetic* females. Bell concluded that if only gangrene due to atherosclerosis is considered, gangrene develops nearly *forty* times as frequently in diabetic as in non-diabetic subjects. If all forms of gangrene of the leg except those *due to trauma and frost-bite were considered, nearly two-thirds of the* females with gangrene have diabetes

Age.—Among 670 cases with onset of diabetes after the age of seventy years treated at the Deaconess Hospital, 69 had gangrene. The frequency was less in those who acquired diabetes a decade earlier, between the ages [illegible] occurrence was

[illegible]

tieth and twenty-ninth year of age, but 190 patients had developed diabetes *between the thirtieth and forty-ninth year. In the same series only* 67 patients were thought to have had diabetes less than one year and 179 cases had had diabetes from one to five years. Sixty-seven per cent of the series had had diabetes from five to forty years

The average age at which the gangrene developed was sixty-four years. Arranged by decades, as is done in Table 107, the percentage distribution according to age at onset of gangrene is still more plainly shown. The

[19] Committee on Diabetes, Mass. Med. Soc.: New England Jour. Med., *253*, 685, 1955.
[20] Oakley, Catterall and Martin: *Brit. Med. Jour.*, *2*, 953, 1956.
[21] Bell: Arch. Path., *49*, 469, 1950.

important feature was the presence of many dissectible anastomoses. Occasionally their diameter approached that of the original arteries they connected. In addition, extensive anastomoses, not visible to the naked eye, were demonstrated by the finding of injection mass distal to all but 19 of 385 complete occlusions. Fresh thrombotic occlusions were present in half the extremities. They were frequently multiple and sometimes several centimeters in length. The frequency and extent of these fresh thrombotic occlusions justified the conclusion that anti-coagulant therapy may come to play an important rôle in the management of patients with early gangrene. Although occlusions were present in each leg in which gangrene occurred, there was a poor correlation between the extent of necrosis on the one hand and the extent of the arterial obstruction, or the extent of the collateral circulation, on the other.

In any patient with narrow or blocked arteries nature attempts to improve matters by developing collateral channels by-passing the diseased area. In diabetic patients this ability is frequently limited, although we do see patients with no palpable pulses below the aorta who have relatively few symptoms.

The rôle of the sympathetic nervous system is difficult to evaluate. Aside from stimulating the sweat glands, activity of the lumbar system narrows the smaller arteries and arterioles of the legs and diverts blood away from the skin and into the muscle. We have observed that many diabetic patients have lost sympathetic activity presumably due to changes in the nerves themselves, have no sweating and, following nerve blocks, have very little change in the skin temperature. The effect of sympathetic activity also depends on the condition of the vessels, since it is difficult to picture a sclerotic small artery altering its diameter to any extent.

Symptoms.—The most important warning symptoms are the result of deficient blood supply or ischemia of the tissues. They may come on suddenly as a result of slowly progressing obliteration of the lumen or develop abruptly as the result of sudden thrombosis. In diabetic patients the development of collateral circulation may go on *pari passu* so that small areas of gradual occlusion have given the patient few symptoms or none at all until a sudden thrombosis occurs.

1. Intermittent claudication usually at first is unilateral. It may exist for years or progress rapidly so that the distance which a patient can walk without pain may be reduced from a few blocks to fifteen yards. The location of pain, depending upon which artery is blocked, may be in the foot, anterior lower leg or calf, thigh, or gluteal area.

2. Rest pain noted particularly at night indicates advanced and severe reduction in blood supply either by an acute process or a gradually progressing one.

3. The pain of ischemic neuritis occurs over a large area and may be present without ulceration. It may be of a burning character, severe and difficult to relieve.

4. Paresthesias consisting of sensations of numbness, deadness in the toes and foot with or without tingling or prickling are common.

5. Coldness of the feet and sensitiveness to cold weather occur commonly

youngest patient to develop gangrene was aged thirty-two years and the age of the oldest patient was eighty-nine years.

Etiology.—Gangrene occurs chiefly in obese patients with diabetes of long standing and low insulin requirement. It is usually precipitated by trivial infections, resulting from trifling traumata, which have been neglected. Epidermophytosis between the toes in recent years has become a predisposing cause of increasing frequency. On account of the impaired circulation of the extremity, due to sclerosed, narrowed and thrombosed vessels, rarely occluded by embolism, even slight infection of calluses, corns or

group. In the fifth decade it was twelve times as common in diabetic as in non-diabetic women. It is to be distinguished sharply from thromboangiitis obliterans which occurs predominantly in males and almost never in diabetics. Probably 20 per cent of all cases of gangrene due to arteriosclerosis obliterans have diabetes.[23] In the arteriosclerotic lesions of diabetes the two sexes are almost equal.

Gangrene occurs because tissue has lost its blood supply and therefore dies. If the flow of blood is suddenly cut off as by an embolus or thrombosis, necrosis may develop rapidly. When the vessel narrows gradually, the changes are slower and the tissues pass through a long stage of ischemia, which is usually painful.

The area of narrowing or blocking may involve the small digital artery or medium-sized arteries, such as the anterior or posterior tibials in the lower leg, it may be in the larger arteries higher up, or be found as a combination of these. In diabetics this process which injures the arteries is arteriosclerosis with thickening of the intima and eventual obliteration.

grene, since tissues which are barely able to survive under normal conditions have little resistance to infection and very poor healing power. With infection there is further thrombosis of small neighboring arterioles and consequent spread of the process.

A new technique for the study of the arterial circulation of amputated extremities and the results of its application in 58 amputated legs were analyzed by Wessler.[24] The method was based on the use of a new radiopaque injection mass containing lead and gelatin and a method of dissection which unfolds the major arteries in one plane. Among the 54 arteriosclerotic extremities there was an average of 9 occlusions of the leg and actually 26 per cent of the length of the major vessels were completely occluded. However, in contrast, very little occlusive disease in either the lateral or terminal branches of the major arteries to the lower leg was found. An

[22] Dry and Hines: Ann. Int. Med., 14, 1893, 1941.
[23] Allen, Barker and Hines: Peripheral Vascular Diseases, Philadelphia, Saunders & Co., 2nd ed., p. 221, 1955.
[24] Wessler: New England Diabetic Assn., May 28, 1951.

of the infection or ulceration This distinction must be made accurately lest amputation be either needlessly performed or unduly delayed.

Prevention [illegible]

At one time, 1 diabetic in 5 who came for hospital treatment after the age of seventy years acquired gangrene and for eighteen years in Boston 1 diabetic in 5 died with it as a contributory cause Already education of [illegible]

few hours at a time, and blisters which may have formed pricked only under aseptic precautions, arch supports should be used with care; corns and toenails are to be cut only after thorough cleansing of the part and with good instruments and in a good light Strong liniments are to be avoided, and the dangers of hot-water bags and heaters made vivid to the patients, a stiff big toe is not uncommon and these patients must be taught to limber up their toes Epidermophytosis must be checked, because it favors deep infections between the toes (See pages 521 and 607) Patients must be instructed and urged to walk for short intervals each day, to go through such gymnastic exercise as will bring about a free flow of blood in the feet and not to remain long in one position The legs are not to be crossed and compressing garters should be avoided Massage is useful Warm foot [illegible] of heat even in the form of [illegible] that with the temperature [illegible]

It is important to bear in mind that the use of heat in any form may hasten gangrene in a foot with deficient blood supply In such a foot, the application of heat increases the rate of metabolism and of oxygen need in a part in which the blood supply cannot keep pace with the increased requirements

Treatment of Feet

The following sheet of instructions has long been given to patients at the New England Deaconess Hospital.

Hygiene of the Feet.

1 Wash feet daily with soap and lukewarm water. Dry thoroughly, especially between toes, using pressure rather than vigorous rubbing

[a] Starr Proc Assn Am Phys, 47, 339, 1932

Physical Examination.—1. *Pulses.*—The palpation of a pulse is the best indication of circulation in the larger vessels at the level examined. Its absence does not mean that a serious deficit in arterial circulation exists since the collateral channels may be adequate. The aorta, iliac, femoral, popliteal, dorsalis pedis, and posterior tibial pulses are normally palpable. *Examination of pulsations should be made at every visit of every diabetic patient beyond middle life.*

2. *Temperature.* Palpation may reveal coldness as the hand is passed down the leg toward the foot. It is important to compare the two extremities.

[illegible]

of the foot (if no varicose veins are present). The veins are emptied by elevation first, and the patient is then asked to sit up with the legs hanging down. The time is noted when the veins first project above the skin surface. If this is more than 20 seconds, there is serious impairment of the circulation to the foot.

5. *Nutrition.*—With prolonged arterial insufficiency, certain changes take place in the various tissues. The skin becomes thin and shiny with fewer hairs [illegible] muscle mass and the subcutaneous [illegible] me osteoporotic. Edema may [illegible] the night sitting up to get relief of pain in the extremity.

Laboratory Studies.—*X*-ray examination may disclose visibly calci- [illegible] obliterans from [illegible] Cal- [illegible] bly [illegible]

Surface temperature measurements after spinal anesthesia and other special tests such as the flare test and the use of the oscillometer have only rarely proven useful.

Differential Diagnosis.—Buerger's disease or thrombo-angiitis obliterans is a rare disease in a diabetic patient. We have not seen it proven by adequate pathologic examination. Pain in the lower extremity may be due to gout, arthritis, neuritis, pronated feet, muscle strain, spinal cord diseases, *etc.* However, the differentiation between arterial insufficiency and these diseases is not usually difficult.

It is important to remember that an open foot lesion in the diabetic patient can be due not only to arterial insufficiency but possibly to infection alone in a foot with good circulation, or to a perforating ulcer or similar destructive lesion developing secondary to pressure in a numb ("neuropathic") foot which has good circulation. In the conditions where the blood supply is good, unless the lesion is far advanced, one can expect to salvage *the extremity by adequate drainage of infection* plus later excision of destroyed areas. Edema may obscure pulses in the foot that could otherwise be felt so that evaluation of the circulation may have to depend on the other physical findings we have described, plus the behaviour

Treatment of Abrasions of the Skin:

1. Proper first-aid treatment is of the utmost importance even in apparently minor injuries Consult your physician immediately
2. Avoid strong irritating antiseptics, such as sulpho-naphthol and iodine.
3. At once after injury some surgeons recommend applications of

   may be purchased at drug stores.
4. Elevate, and, as much as possible until recovery, avoid using the foot
5. Consult your doctor for pain, redness, swelling, or any inflammation

Calluses, Corns, Warts and Fungus Infections —Calluses and corns are common lesions and frequently the site of infection leading to osteomyelitis, a sequence of events almost pathognomonic of diabetes. The lesions themselves result from pressure from excessive body weight, from badly fitting shoes or a combination of the two The most serious lesions are the infected calluses and corns or warts where a neurogenic background prevents the existence of much pain Calluses and corns should be relieved of pressure and especially be protected by the shields which a competent chiropodist can provide Patients should be warned against cutting such lesions with any sharp instrument unless they can use such an instrument under aseptic precautions equal to that of the surgeon Corns that are hard occur chiefly on the external surfaces of the fifth toes The soft corn seen between the other toes is frequently an evidence of epidermophytosis. The so-called neurovascular corn containing nerves and blood vessels is painful The plantar wart, due as is true of warts on the hand probably to a filterable virus, is often infected and may prove a serious lesion Strict cleanliness, relief from pressure, drying of the skin and periodic supervision by a trained chiropodist are helpful

Epidermophytosis or fungus infections, often called ring worm or athlete's foot infection, are of great importance in diabetes not because the infection itself is so serious but because it often provides a portal of entry for more virulent pyogenic organisms Injury of the lesion, pressure, and excessive perspiration invite trouble Cultures of the skin are often of benefit Appropriate antiseptic solution, frequent bathing, drying and the use of dusting powder are important Other forms of treatment include weak solutions of potassium permanganate or of aluminum acetate

Night Cramps —Cramps in the legs in a diabetic patient may require careful examination and study with reference to the blood supply to the leg muscles, the condition of the nerve supply and especially the condition of the diabetes itself If no evidence of a nervous disturbance is present and if good pulsations in the arteries as well as other evidence of good blood supply are present, then changes in the diabetic status may underlie the condition In some patients cramps in the legs occur if the blood sugar falls too low during the night Such patients do better if they have a bedtime lunch and may even require food when awakened by the cramps

2. When thoroughly dry, rub with lanolin as often as necessary to keep skin soft and free from scales and dryness, but never render the feet tender. If the feet become too soft, rub once a day with alcohol.
3. [illegible]

   in a good light and after a bath, when the feet are clean Cut the nails straight across to avoid injury to the toes, and do *not cut the nails too short. If you go to a chiropodist, tell him you have diabetes.*
4. All patients with overlapping toes or toes that are close together should separate them by lamb's wool. Patients with large joints or cramped-up toes should wear shoes without box toes and only vici kid leather.
5. All patients over sixty years should have daily rest periods and remove their shoes. Every Sunday morning ask someone to examine your feet.
6. Do not wear bedroom slippers when you ought to wear shoes. Slippers do not give proper support Do not step on floor with bare feet
7. Wear shoes of soft leather which fit and are not tight (neither narrow nor short). Wear new shoes one-half hour only on the first day, increasing one hour daily.
8. Use bed socks instead of hot water bottles, bags, bricks or electric heaters
9. *After fifty years one hears less well, sees less well, and the sense of* feeling is diminished. Remember this and be cautious about the feet.

Treatment of Corns and Calluses:

1. Wear shoes which fit and cause no pressure.
2. Soak foot in warm, not hot, soapy water. Rub off with gauze or file off dead skin in or about callus or corn. Do not tear it off. Do not cut corns or calluses. Do not try to remove corns or calluses with patent or other medicines.
3. Prevent calluses under ball of foot
   (*a*) by exercises such as curling and stretching toes twenty times a day.
   (*b*) by finishing each step on the toes and not on the ball of the foot

Aids in Treatment of Imperfect Circulation —Cold Feet:

1. Exercises Bend the foot down and up as far as it will go six times. Describe a circle to the left with the foot six times and then to the right Repeat morning, noon and night
2. Massage with lanolin or cocoa butter.
3. Do not wear circular garters or sit with knees crossed
4. If you have had gangrene or been threatened with it, keep off your feet five or more minutes each hour of the day, and if an amputation, fifteen or more minutes

New England Deaconess Hospital They also supervise the "Beauty Parlor for Diabetic Feet" given the hospital by Mr. and Mrs William L. Shearer in which Dr John Kelly and Dr. I. Malcolm Humphrey are the chiropodists.

Treatment.—When the diabetic patient is found to have evidences of deficient blood supply in the extremities due to arteriosclerosis obliterans plans of treatment must be adjusted according to the individual need. It *must be remembered that arteriosclerosis obliterans is that form of arteriosclerosis* found in the legs of diabetic patients which tends to progressive occlusion of arterial lumina. Although the atheroma characteristically is most extensive in the larger arteries nevertheless the development of extensive collateral pathways occurs and the encouragement of this collateral circulation is [illegible]
patient In [illegible]
must be stud [illegible]
eyes In addition to the atheromatosis of larger arteries the extensive involvement of small arterioles with hyaline and fibrous change and the particular danger of slight trauma and infection are important factors in the course of the disease The following outline summarizes methods commonly applied

1 *Claudication* —Frequently the first sign of arterial disease is pain in the calf muscle on walking This is usually due to occlusion of the lower femoral artery in the adductor canal but may be due to narrowing of the smaller arteries in the lower leg itself Where the symptoms are mild or or if the patient is a poor risk by reason of cardiac, renal or other disease, the treatment should consist of limitation of activity, good diabetic control, a low fat diet, omission of tobacco, postural (Buerger) exercises, and careful care of the feet to prevent the development of areas of gangrene.
[illegible]

years of age It usually does not greatly relieve the claudication but will increase circulation to the skin and may thereby protect against gangrene of the skin in the [illegible]
ance We try to [illegible]
and who have sign [illegible]
discernible skin [illegible]
evaluate the results of sympathectomy since so much must depend on subjective observation and on long-term follow-up with great difficulty in obtaining a good control group for comparison, (Table 108) In the small group who have had this procedure at the New England Deaconess Hospital, the results have been best in the younger age group (20 to 50 years of age) and in those who had pulses in the foot or in the popliteal artery

The second dire[illegible] ar the more effective, is [illegible] pulse cannot be felt the [illegible] it. If there is open artery below this block of sufficient size, an artery graft may be placed to by-pass the block and re-establish the circulation To deter-

More commonly cramps are associated with an increase in the sugar in the blood, and then extra insulin taken at bedtime in addition to the usual insulin dose may help. *Thus the patient who is taking protamine zinc*

become

ing in a

that the

taking of quinine sulphate, grains 5, six nights a week, will prevent cramps

In some diabetic patients, preparations for the night should include lying down for ten or thirty and sixty minutes once or twice during the course of

he Buerger

gives sur-

w minutes

during the evening once or twice may be helpful, thus avoiding a fixed position for a long period of time. For many people the cramps when they occur are relieved by exercising the muscles

The feet should not be cold at night, and therefore many patients do better if they wear bed socks or even stockings which come to the knee The legs should be kept straight rather than at a sharp angle It is often desirable for patients to sleep with the head raised on a fairly high pillow, or better still, raise the legs of the bed. For some patients the taking of calcium gluconate, grains 10, two or three times a day, seems to be helpful

Buerger[26] suggested that certain passive exercises may be of value in inducing hyperemia or rubor in the affected limb, and therefore, therapeutically beneficial in increasing the blood supply. If the method is carried out daily for a long period, it is of great value in improving the circulatory conditions and in increasing the blood supply

Buerger's Passive Exercises.—"The affected limb is elevated with the patient lying in bed, to from 60 to 90 degrees above the horizontal, being allowed to rest upon a support for thirty seconds to three minutes, the period of time being the minimum amount necessrry to produce blanching or ischemia As soon as blanching is established, the patient allows the foot to hang down over the edge of the bed for from two to five minutes, until reactionary hyperemia or rubor sets in, the total period of time being about one minute longer than that necessary to establish a good red color. The limb is then placed in the horizontal position for about two to five minutes The placing of the limb in these three successive positions constitutes a cycle, the duration of which is usually from six to ten minutes These cycles are repeated over a period of about one hour, some six to seven *cycles constituting a seance* "

The Buerger boards as used at the New England Deaconess Hospital consist of two boards, each ¾ inch thick, 30 inches long, and 11 inches wide, hinged at one end In the middle of one board is a hinged tongue with a cleat on the other board so that the boards can be opened at an angle of 30 degrees, 45 degrees or 60 degrees as desired Patients may spend from three to six hours daily in doing these exercises

So convincing are the effects of treatment that special nurses have been placed in charge of the care of the feet of all the surgical diabetics at the

[26] Buerger Surgical Diagnosis and Treatment by American Authors, edited by A J Ochsner, Philadelphia, Lea & Febiger, 4, 810, 1920

metatarsal, saving part of the foot, is not indicated except under the most unusual circumstances

3 *Gangrene* —This complication may be secondary to infection in the presence of good circulation, in which case proper antibiotics, drainage, and excision will usually save the foot. More commonly areas of gangrene develop due to impaired circulation If gangrene is present and pulses are present in the foot or in the popliteal area, measures to improve the circulation will include rest, Buerger exercises if there is not active infection, and consideration of sympathectomy as previously discussed Secondary infection is treated by drainage of any pockets of pus and antibiotics When the process has subsided, the infection become localized and pain

weeks of hospital bed rest or if the circulation is too poor, probably a leg amputation will be indicated

(*a*) *Distal Third of Toe* —Where the actual destruction has spared enough proximal normal skin to permit a simple toe amputation through the proximal phalanx, in most instances medial and lateral flaps for closure are used If the circulation is poor, this operation may be unwise and a more proximal operation such as a transmetatarsal amputation is preferable If one does a simple toe amputation which fails, it is not always possible to salvage the situation by performing a transmetatarsal amputation, because infection may have spread proximally, destroying too much tissue. We have not considered disarticulation amputations safe or satisfactory at any level

The first toe is more difficult to handle as it is so broad that the flaps have to be quite long and therefore, more prone to necrosis. For this reason a transmetatarsal amputation is more often considered for lesions of this toe than for the others If multiple toes are involved in the presence of questionable circulatory adequacy, we are apt to turn to the transmetatarsal amputation

(*b*) *Gangrene of Proximal Toe* —Here there can be no question of a simple toe amputation as there is not sufficient remaining skin for closure If the first or fifth toe is involved, it may be possible to remove a toe and metatarsal head through a racquet incision The alternative procedure is the transmetatarsal amputation removing all toes proximal to the metatarsal heads and obtaining closure by use of a plantar flap carried up over the end of the foot The latter procedure in our experience is preferable in that it heals more promptly.

(*c*) *Gangrene of Web Spaces or of Skin Over First or Fifth Metatarsal Heads* Here the only possible conservative operation is the transmetatarsal amputation This method is the one way where enough skin for closure can be obtained.

(*d*) *Gangrene of Foot, dorsum or plantar areas* —In this condition, if caused by arterial insufficiency, there is little hope of saving the extremity If the necrosis, or coldness, does not extend above the ankle and if the

mine whether such a situation exists, a femoral arteriogram is performed

the small number of diabetic patients who are candidates for artery grafting. Some patients with a good anatomic condition for a graft have so much coronary artery disease that it is not warranted However, we have successfully operated on a small number of these patients, as will be discussed later

TABLE 108 —SYMPATHECTOMY IN DIABETIC PATIENTS

Result	Necrosis	Indication Rest Pain	Claudication	Total
Good	16	7	8	31
Fair	13	3	4	20
Poor	21	4	4	29

Never dispair of helping the patient with intermittent claudication. Occasionally the pain at night is relieved by 5 grains of quinine sulphate taken regularly after the evening meal One patient whose intermittent claudication was worse in the daytime has been relieved by 15 grains of quinine sulphate daily for months

2 *Rest Pain* —This symptom indicates more serious arterial insufficiency than does the occurrence of claudication alone. Of course one must distinguish the pain of neuritis and other causes from the pain of ischemia. Night rest pain is commonest due in part, at least, to the normal slowing of circulation at night plus the horizontal position of the patient in bed with no aid to the circulation from gravity

Treatment of this symptom and its cause may follow several courses

(*a*) *Conservative Management* —In many patients rest pain develops because of some new block in the circulation which in time will be alleviated through the development of collateral circulation Thus a period of ... worth while Elevation

... for as long

... and care of

... the results

from vasodilating drugs and seldom use them

(*b*) *Operative Procedure* —The indications for sympathectomy are as

graft in view.

If rest pain is sufficiently severe due to marked arterial insufficiency and the above procedures are not indicated, an amputation may be required Whether this is below or above the knee will depend on the circulation and the patient's general condition. An amputation such as a trans-

tion has been most satisfactory as seen in Table 111 Initially all amputations in this group were successful

The patients with arterial insufficiency comprise the larger group,

to determine how well they continued. The results indicate that the operation is worth while, saving many legs, and with lasting benefit for an appreciable length of time, Table 113

TABLE 109 —TRANSMETATARSAL AMPUTATIONS

Group I (Neuropathy-infection)	67	15 5%
Group II (Arterial insufficiency)	366	84 5%
	433	
Postoperative Deaths	5	1 2%
Initial Success	360	83 0%
Early Failure	68	15 8%
Total Cases	433	

TABLE 110 —AGE AT OPERATION

Years	*Neuropathic*	*Arterial Insufficiency*
21-30	1	0
31-40	3	2
41-50	7	17
51-60	32	95
61-70	16	163
71 and over	8	89

TABLE 111 —GROUP I—RESULTS

(Neuropathy-Infection)

Died postoperatively	1
Died subsequently	22
Late Failures	5
Lost	10
Currently Successful	29
Total	67

Table 112 evaluates the circulation as represented by palpable pulses Table 114 records the patients whose amputations failed, while Table 115

tions higher up on the limb When successful, the patients wore regular shoes with a stiff sole, lambs wool or sponge rubber fillers in the toes, and walked without limping

to perform and later it is much more difficult to fit and use a prosthesis

(e) *Gangrene of the Heel.*—This is of very common occurrence, frequently developing after confinement to bed. Hence we try to protect our patients when they are in bed for any period of time through use of a thin pillow placed beneath the lower legs to keep pressure off the heels. Conservative treatment of this lesion on a semi-ambulatory basis through many months is often successful Excision and grafting have been attempted and proved so unsuccessful that we have given them up Occasionally, the process extends or becomes so painful that amputation is necessary.

J. TRANSMETATARSAL AMPUTATION

Although the emergency character of infectious or gangrenous lesions of the toes and feet of diabetic patients has long been recognized, a new aspect of this problem is presented by the demonstration that in many diabetic patients a useful and serviceable foot can be preserved through the proper use of transmetatarsal amputation.[27,28] Success in the use of this procedure *is dependent upon the early recognition of the essentially progressive character of the underlying vascular disease and early hospitalization of the patient for study and, if necessary, amputation at the optimal moment*

A considerable number of diabetic patients have circulatory, neurologic, or orthopedic conditions in their toes such that an open lesion on one toe will be followed within months or a year by recurring lesions on other toes The chief cause of the lesion in the toe is deficient blood supply due to arteriosclerosis, but complicating factors may be rigid arthritic joints and impaired sensations due to diabetic neuropathy

The transmetatarsal amputation is done for the following indications. (McKittrick)[29]

1 Gangrene of all or part of one or more toes providing that the gangrene and accompanying infection have become stabilized and the gangrene has not involved the dorsal or plantar aspect of the foot

2 A stabilized infection or open wound involving the distal portion of the foot when total excision of the infected area with primary or delayed closure can be accomplished

3 An open infected lesion in a neurogenic foot (*a*) as a curative procedure when the entire area of anesthesia can be excised, or (*b*) as a delaying procedure when the area of infection can be excised, but the line of incision is through the area of anesthesia

at

suc...

shown in Table 110

The operation performed for neuropathy or infection with good circula-

[27] McKittrick New England Jour Med *237*, 929, 1946
[28] Root Ibid , *239*, 453, 1948
[29] McKittrick, McKittrick and Risley Ann Surg , *130*, 826, 1949

loss, the remaining leg has to carry more of the load when the patient walks with his artificial leg and not infrequently fails to stand the added strain. This danger is real and therefore, everything possible must be done to guard against it It is also important to point out that a blind person rarely can use an artificial leg Since failing vision is not uncommon in the elderly diabetic, we frequently meet this tragic combination

Not too many years ago major amputations were accompanied by an astounding mortality, often as high as 50 per cent and largely due to complications related to the control of the diabetes, anesthesia and sepsis One by one these problems were overcome In 1934, McKittrick and Pratt found the mortality to be 14.1 per cent and predicted that if infection could be controlled by medicines the mortality due to unavoidable events such as coronary occlusion, cerebrovascular accidents, or renal failure would be 4 7 per cent This has been proved now that infections from thigh amputations are so rare, due to the use of antibiotics For the six years 1951–1956, there were 16 deaths among 261 above or below the knee amputations, which gives a mortality rate of 6 1 per cent.

Lower Leg Amputations —With increasing frequency we have utilized this procedure rather than a supracondylar amputation since the patient with his own knee joint can walk so much more efficiently than the patient who has lost it Simply stated, a below-knee amputation is performed when conditions require loss of the leg in a patient. (a) whose lesion does not extend above the ankle, (2) when there is no coldness of the skin above the ankle, and (3) when the patient's general condition seems to indicate that he would utilize the amputation Lower leg amputations in 1956, constituted 50 per cent of the major amputations

This technique is quite standard Enough length must be left below the knee to give leverage to move the prosthesis Anterior and posterior short flaps are used The fibula must be divided at a higher level than the tibia, which must in turn be beveled anteriorly Great care of the thin anterior flap is essential and it must not be elevated further up the leg than necessary Only the fascia and skin are closed over the bone ends, avoiding tension The procedure is most easily accomplished with the patient prone and the knee flexed Due to the characteristics of the stump, walking with a prosthesis is not possible as early as with the supracondylar amputa[illegible]

of five [illegible]

Low[illegible]

is reserved for patients who require a major amputation and who for the reasons mentioned previously are not candidates for a below-the-knee procedure Indeed, there is rarely any necessity of going as high as the mid or upper thigh and such levels make the fitting and usage of artificial limbs most difficult

The technique of operation is simple A circular incision is used and carried through all layers The femur is divided high enough to permit easy closure which is carried out by closing the fascia and skin transversely. There is no weight bearing on this nor pull on the incision so that early

* Pratt Bull New York Acad Med, 26, 780, 1950

TABLE 112.—LOWEST PALPABLE PULSE—(ARTERIAL INSUFFICIENCY GROUP)

Lowest Pulse	Total Group		Early and Late Failures	
		Per Cent		Per Cent
Aorta	3	0.8	1	0.8
Femoral	179	48.9	68	51.8
Popliteal	162	44.4	48	38.7
Pedal	18	4.9	5	4.0
Not recorded	4	1.1	2	1.6
	366		124	

TABLE 113.—RESULTS IN ARTERIAL INSUFFICIENCY GROUP

Postoperative Deaths	4
Subsequent Deaths (Amputation healed)	134
Failed	120
Unhealed Currently	2
Lost	18
Alive and Healed	88
	366

TABLE 114.—FAILURE (ARTERIAL INSUFFICIENCY GROUP)

	No. Cases
Postoperative Deaths	4
Immediate Failure (within 1 month)	68
Failure (less than 1 year)	6
Failure (1 year)	25
Failure (2 years)	6
Failure (3 years)	5
Failure (4 years)	3
More than 5 years	7
Total	124

TABLE 115.—SUCCESSFUL OPERATIONS

Time from Operation	Total Patients	Successful Result	Per Cent
1 year	317	218	69
3 years	255	156	61
5 or more years	174	87	50

Careful preoperative preparation to localize the process cannot be over emphasized. We frequently spend one to three weeks in accomplishing this with the patient hospitalized and on strict bed rest with the previously mentioned measures of conservative management.

K. MAJOR AMPUTATION

Unfortunately, amputation of a lower extremity in the diabetic patient remains relatively common. Aside from the disadvantage of the immediate

loss, the remaining leg has to carry more of the load when the patient walks with his artificial leg and not infrequently fails to stand the added strain This danger is real and therefore, everything possible must be done to guard against it It is also important to point out that a blind person rarely can use an artificial leg. Since failing vision is not uncommon in the elderly diabetic, we frequently meet this tragic combination

Not too many years ago major amputations were accompanied by an astounding mortality, often as high as 50 per cent and largely due to complications related to the control of the diabetes, anesthesia and sepsis One by one these problems were overcome. In 1934, McKittrick and Pratt found the mortality to be 14.1 per cent and predicted that if infection could be controlled by medicines the mortality due to unavoidable events such as coronary occlusion, cerebrovascular accidents, or renal failure would be 4 7 per cent. This has been proved now that infections from thigh amputations are so rare, due to the use of antibiotics For the six years 1951–

[illegible]

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stituted 50 per cent of the major amputations

This technique is quite standard Enough length must be left below the knee to give leverage to move the prosthesis Anterior and posterior short flaps are used The fibula must be divided at a higher level than the tibia, which must in turn be beveled anteriorly Great care of the thin anterior flap is essential and it must not be elevated further up the leg than necessary Only the fascia and skin are closed over the bone ends, avoiding tension The procedure is most easily accomplished with the patient prone and the knee flexed. Due to the characteristics of the stump, walking with a prosthesis is not possible as early as with the supracondylar amputation, the average period prior to ambulation being in the vicinity of five weeks for the former and two and a half weeks for the latter

Low Thigh Amputation —The low thigh, or supracondylar amputation is reserved for patients who require a major amputation and who for the reasons mentioned previously are not candidates for a below-the-knee procedure Indeed, there is rarely any necessity of going as high as the mid or upper thigh and such levels make the fitting and usage of artificial limbs most difficult

The technique of operation is simple A circular incision is used and carried through all layers The femur is divided high enough to permit easy closure which is carried out by closing the fascia and skin transversely There is no weight bearing on this nor pull on the incision so that early

[illegible] Pratt Bull New York Acad Med, *26*, 786, 1950

use of a prosthesis is possible and desirable Most of the patients are elderly and walk with the knee of the prosthesis locked so it cannot bend.

L. ARTERY GRAFTS

Since 1952, we have been interested in replacing, or by-passing occluded segments of artery in the lower extremity by use of ...

i ... in the smaller arteries where grafts are not possible Many of the others were too poor risks due to cardiac, renal or cerebrovascular ...

Those ...

general ... on the femoral, were studied by femoral arteriograms as previously described. Local anesthesia ...

... the groin so that femoral arteriography is sufficient and much safer than aortography

Among arteriograms performed on diabetic patients, selected as outlined above, only 27 were found suitable for artery grafting At first the operation selected was resection and replacement by a graft of the occluded segment which is usually in the adductor canal just above the knee Either an autogenous saphenous vein or a homologous artery graft[ll] was used to bridge the gap, using end-to-end ...

frequently narrow ...

longer grafts were ...

of the patient's artery

TABLE 116 — ARTERY GRAFTS

	End-to-End	*End-to-Side*
Died Postoperatively	2*	0
Died Subsequently (Grafts open)	3	1
Immediate Thrombosis	3	0
Delayed Thrombosis	3	2
Open until lost	3	0
Open to present	0	9
Open until amputation	0	1†

* Both died of coronary occlusion prior to discharge from the hospital
† Graft successful but prior gangrene too advanced to save leg and a below-knee amputation was performed

The results by this method were discouraging Of 14 cases, only 6 lasted long enough to be worthwhile to the patient, Table 116

l Artery grafts were obtained at post-mortem, frozen and sterilized by cathode rays, as described by Meeker and Gross

ll Meeker and Gross Science, *114*, 283, 1951

In the Spring of 1954, Mr. Frank Cockett of London introduced us to his modification of the Kunlin[37] technique of performing end-to-side grafts, by-passing the narrow or occluded host artery. This enabled us to utilize the common femoral or external iliac artery proximally without dividing it, thus obtaining a better head of pressure for the graft and at the same time preserving any and all of the patient's arterial tree that could be utilized. The grafts currently are usually quite long, running from the groin to the knee, 40 to 50 cm. Another advantage of this method is that the softest part of the artery can be selected for the anastomosis, usually the anterior wall The anastomosis itself is easier technically and there is no narrowing of the lumen, an unavoidable disadvantage of the end-to-end anastomosis

Table 116 indicates how much more satisfactory a procedure this has been There were no initial failures and only two grafts have closed subsequently. Five of the nine open grafts have now gone two years or more since operation In 11 of the 13 patients, the indication for operation was rest pain

established, but the situation favorable for grafting in these patients unfortunately, is not frequent due to the diffuse nature of their arterial disease

M. FRACTURES AND DIABETES

osteoporosis have occurred A crushed vertebra has been found following a convulsion due to insulin hypoglycemia in 2 cases Recognition of postural hypotension in diabetic neuritis is important, dizziness has led to a fall and fractured hip in at least 1 case at the New England Deaconess Hospital Patients under care in hospitals especially with foot lesions who are having limited exercise, because of unsteadiness and weakness, may slip either getting into bed or when rounding a corner Instances of fractured skull, fractured coll...

Wh

calc

patient, (2) activity, (3) amount of lime salts in the diet, (4) great excess

absorbed, and (9) deficient supply of vitamin D

foi

gr

[37] Kunlin Arch Mal Coeur, 42, 371, 1949
[38] Root, White and Marble Arch Int Med, 53, 16, 1934

N. BURNS

Thermal injury to the skin and underlying tissues may have grave consequences in a diabetic. Experimentally, Clark and Rossiter[34] found

lactacidemia and lowered carbon dioxide combining power of the blood in normal human subjects after thermal injuries.

On a single day, among 15 diabetics in the New England Deaconess Hospital ward for surgical lesions of the feet, 10 had been burned by hot soaks, hot water bottles or heating cradles.

Two diabetics treated at the Deaconess Hospital illustrate the most severe effects of thermal injury.[36] In an elderly housewife with mild dia-

man received a sunburn which became infected with resultant paranephric

whereas in diabetic patients the lack of insulin reserve makes possible the rapid development of serious disturbances in carbohydrate metabolism and even acidosis

When a surgical diabetic is not doing well, do not blame the diabetes The

[34] Clark and Rossiter Quart Jour Exper Physiol, 32, 279, 1944
[35] Taylor, Levenson and Adams New England Jour Med, 231, 437, 1944
[36] Root Ibid, 232 279, 1945

Chapter 26

CLINICAL DISORDERS OF THE GLANDS OF INTERNAL SECRETION COMPLICATING DIABETES

HOWARD F. ROOT, M.D., AND ROBERT F. BRADLEY, M.D.

REFERENCE has been made repeatedly throughout the text to the close interrelationship between the various glands of internal secretion and the influence, particularly of the pituitary, thyroid, and adrenal glands upon diabetes. The outstanding feature is the homeostatic or regulating effect of both the anterior pituitary and the adrenal cortical hormones. Certain hormones of each have a diabetogenic effect when administered in excess. (See page 124) A number of clinical states may produce a disturbance in the dynamic balance between the rate of insulin production by the pancreas and the rate of insulin requirement by the tissues. The results may be insulin resistance on the one hand or insulin sensitivity and frequent hypoglycemic reactions on the other.

A. THE ANTERIOR PITUITARY AND DIABETES

Various clinical symptoms, including the tendency of diabetic children to be above height for their age at onset of diabetes, the development of their bones a year in advance of their age, the glycosuria of pregnancy, the hormonal disturbance in the toxemia of diabetic pregnancy, (See Chapter 28, p. 704), and the onset of diabetes at the menopause suggest that abnormalities in pituitary function may play a part in the development and course of diabetes.

Hyperpituitarism. Acromegaly is a chronic disease characterized by progressive overgrowth of many tissues in response to the stimulation by the growth hormone of the pituitary body. The name indicates the striking enlargement of the acral or terminal portions of the body, the hands, feet and portions of the face and head. Increased production of growth hormone prior to normal ossification of usual epiphyseal cartilages may result in gigantism. The cause of acromegaly and the gigantism associated with it is hypersecretion from neoplastic or hyperplastic eosinophile cells of the anterior lobe of the pituitary body. The major effects are those due to the growth hormone, although in some cases increase of all anterior pituitary hormones occurs.[1]

[1] Williams Textbook of Endocrinology, 2nd ed., Philadelphia, W. B. Saunders Co., p. 65, 1955.

(*a*) Incidence of Glycosuria in Acromegaly.—The concept of the connection of the pituitary with the pancreas is strengthened by the fact that in disease of no other organ save the pancreas are glycosuria and diabetes so common. In 100 cases of proved acromegaly, Davidoff and Cushing[1a] found glycosuria in 25 per cent and diabetes in 12 per cent. Coggeshall and Root,[2] in a follow-up of these 100 cases with an addition of 53 later cases of acromegaly made possible through the courtesy of the late Professor Harvey Cushing and the Peter Bent Brigham Hospital, found that actually the incidence of glycosuria was 36 per cent. Analysis of these cases is given in further detail in later pages. Among these 153 acromegalics, 26, or 17 per cent, developed diabetes.

(*b*) Character of Diabetes in Acromegaly.—*The common impression* is that the diabetes which is found in connection with acromegaly or other pituitary disease does not differ essentially at any given date from ordinary diabetes,[3, 4, 5] but that it varies from time to time according to the activity of the pituitary and in consequence a spontaneous, temporary or permanent cure of the diabetes may be effected. Practically the only temporary or permanent cures of diabetes recorded are those cases in which a pituitary factor has been present. The article by Davidoff and Cushing is replete with suggestive evidence.

Among these 29 cases of acromegaly with diabetes reported by Coggeshall and Root (26 from Cushing's series and 3 from the New England Deaconess Hospital), certain features stand out. Since acromegaly is often a fluctuating but progressive disease, usually of long duration, the time interval between the onset of acromegaly and the onset of diabetes might indicate to some degree the influence of hyperpituitarism as an etiological factor in diabetes. Also, the effects of treatment, either surgical or by means of roentgenray, in contrast to those patients receiving no treatment, might be significant. The evaluation of treatment, however, was difficult, since in cases presenting intracranial pressure, a high mortality-rate interfered with the period of observation. The average interval between the onset of acromegaly and that of diabetes was 9.5 years, but there were actual intervals of from one to twenty-two years with a majority of cases of diabetes occurring within fifteen years. In this series, 10 cases had some *treatment directed toward the pituitary gland, but no characteristic* difference in the time of appearance of diabetes in these cases was evident. Ten were males and 19 females, the average age at onset of diabetes was 38.3 years in both males and females, an age quite different from the median age at onset of 6357 diabetics, for whom it was 46.5 years for males and 49.2 years for females. The duration of the diabetes from onset to death or last observation varied from none to seventeen years, with an average of 8.6 years. Jews form 27 per cent of the acromegalic series, in

[1a] Davidoff and Cushing. Arch. Int. Med., *39*, 757, 1927.
[2] Coggeshall and Root. Endocrinology, *26*, 1, 1940.
[3] Colwell. Medicine, *6*, 1, 1927.
[4] John. Arch. Int. Med., *37*, 489, 1926.
[5] Yater. Ibid., *41*, 883, 1928.

contrast to the Jewish percentage of 11 6 per cent for all males and of 16 3 per cent for all females in the series of 6357 diabetics [6a]

A history of diabetes in the family was obtained in 6 of the 29 cases, whereas in the acromegalics without diabetes a family history of diabetes was found in only 3 of 124 cases The clinical course of the diabetes varied greatly. Three of the 16 fatal cases are known to have died in coma Twelve individuals in this series displayed no evidence of sterility, although it must be admitted that most of the children of these patients were born in the early years after the onset of the acromegaly The common complications of diabetes were frequent Arteriosclerosis and pyogenic infections occured in 7 of the cases, thyroid enlargement was a common finding One case had a thyroidectomy performed because the basal metabolism was plus 74 per cent Dietary management was difficult because of the remarkable polyphagia present in some cases In general mere restriction of carbohydrate seemed to have little effect on the fasting blood sugar However, as a whole, the severity of the diabetes observed, while varying in degree, showed no greater variations than are seen in a large diabetic clinic, as was also true of Wilder's cases [6]

The opinion that acromegalic diabetes does not differ essentially from ordinary diabetes has been challenged by several workers, including Davidoff and Cushing,[7] Hantschmann,[8] Lucke[9] and Meythaler and Schroff [10] The action of insulin was thought to be normal by many other writers, including Blum and Schwab,[11] Colwell,[12] Labbé, Escolier and Dreyfus[13] and Peremy [14]

The possibility that hyperpituitarism may exist for brief periods or without obvious evidences and may thus be the cause of the diabetes, must lead to a thorough search for symptoms and signs Coggeshall and Root tabulated 100 cases of acromegaly and 100 cases of diabetes with a comparison of the symptoms and signs recorded in the two groups It is evident that certain symptoms, such as the disturbances of the menstrual cycle, headaches, diminished libido, amenorrhea, increased basal metabolism, visual disturbances, excessive perspiration, obesity and polydipsia occur with rather striking frequency in both conditions However, until more accurate diagnostic procedures are known, we can only entertain suspicions as to the actual faults of the pituitary in cases that do not show the outspoken evidences of overgrowth of skeleton or soft tissue

(c) Weight of Visceral Organs in Acromegaly and Diabetes — The clinical course of acromegaly has been divided into three periods by Davidoff (1) the early period with general overgrowth, gain in weight and menstrual disturbances, (2) the middle period with neighborhood symptoms from pressure, visual disturbances, increases in the sella turcica, and (3) the final period with polyphagia and polydipsia, etc, due to

[6] Wilder pp 263, 264, loc cit, p 71
[6a] Joslin et al P 50, Loc cit p 416
[7] Davidoff and Cushing Loc cit p 620
[8] Hantschmann Deutsch med Wchnschr 60, 498, 1934
[9] Lucke Ztschr f klin Med 122, 23, 1932
[10] Meythaler and Schroff Klin Wchnschr, 14, 803, 1935
[11] Blum and Schwab Compt rend Soc de biol, 59, 195, 1923
[12] Colwell Loc cit p 620
[13] Labbé, Escolier and Dreyfus Ann de méd, 29, 722, 1931
[14] Peremy Klin Wchnschr, 14, 92, 1935

visceral splanchnomegaly and secondary effects upon the other endocrine organs. The splanchnomegaly of acromegaly is a true overgrowth of all tissues and not due merely to laying down of excess fat or to increased water in the tissues. It is assumed that the enlargement of acra as well as the splanchnomegaly is due to excessive production of a growth hormone or hormones secreted by the acidophilic cells of an anterior pituitary adenoma

pancreas and the weight of other organs of diabetic patients as occurred in acromegaly. To test this hypothesis, Coggeshall and Root[15] therefore, tabulated the weights of tissues in 11 acromegalic patients, together with the weights of tissues in groups of diabetics and in cases of Simmonds' disease (hypophyseal cachexia).

The *striking features* in the diabetic group were the lack of correlation between the weight of the pancreas and the weight of the heart, liver, kidneys, *spleen or thyroid. As a matter of fact, in the first group of* diabetic patients with large pancreases the average weight of the liver, *1978 grams, is due to the inclusion in this group of 6 patients who had a* definite reason for congestion and enlargement of the liver, including chronic cardiac failure and cirrhosis of the liver. In contrast 2 cases of Simmonds' disease showed great reduction in weight of all organs.

From this comparison of the actual weights of organs in diabetes and pituitary disease, *one must conclude that there is no suggestion of any* influence upon the weight of tissues of the diabetic patient by any sub*stance such as is responsible for the enlargement of the skeleton and the*

of acromegaly or gigantism in ıcromegalı and 3 of gigantism have occurred in some 30,000 diabetic patients. On the other hand, 17 per cent of 153 acromegalic patients developed diabetes.

(*d*) Effect of Irradiation of the Pituitary Gland.—Pijoan and Zollinger[16] *studied the carbohydrate metabolism of patients undergoing* massive radiations of the pituitary regions because of the menopausal *syndrome before and after the radiations.* Ten patients, whose ages varied from twenty-nine to fifty years, received a total of 1400 to 1600 R *skin doses over a period of fourteen days. Their blood sugar curves were* obtained after the oral administration of 1 gram dextrose per kilogram body weight. The results showed no essential difference between the curves obtained before the radiation and after. They conclude, then, that such radiation of the pituitary gland caused no change whatever in *carbohydrate* metabolism.

On the contrary, in cases of acromegaly, irradiation of the pituitary may *arrest progression of the disease* with improvement of vision, return of patient's capacity for work and improvement in carbohydrate metabo-

[15] Coggeshall and Root: Loc. cit., p. 620.
[16] Pijoan and Zollinger: Endocrinology, *21*, 357, 1937.

lism.[156] In a 57-year-old female, Pfeiffer[158] reported that, after radiation of the pituitary for acromegaly, the former requirement of 40 units of insulin ceased and glycosuria disappeared even on a free diet.

(*e*) EFFECT OF ESTROGENS.—*Attempts have been made to suppress the activity of the anterior lobe of the pituitary gland and thereby to reduce the severity of human diabetes by the administration of estrogenic substances. In depancreatized dogs some diminution in the glycosuria following such estrogenic substances has been reported.* Attempts to treat diabetic patients with such injections of estrogenic substances have met with slight or indifferent success. At present, although evidence that the administration of such substances, capable of depressing one function of the pituitary, has any significant effect on human diabetes mellitus is slight, the experiments of Houssay indicating the beneficial effects of estrogens in alloxan diabetes of rats are encouraging. (See page 61.)

Illustrative Cases.—In addition to the 29 cases reported by Coggeshall and Root, *six new cases have been observed. In the following patient, even at autopsy, a discrepancy appeared between the staining reactions in a pituitary tumor and the other evidences of acromegaly.* Case 17969, male, aged forty-four at onset of diabetes in 1936, *first came for treatment* in coma in 1939. His maximum weight had been 245 pounds, height 5 feet 10 inches. His weight after recovery was 187 pounds dressed. He required 254 units of insulin. He returned to the hospital on August 13, 1940, because of a large carbuncle. Again he was in acidosis with a blood sugar of 380 mg. and a CO_2 combining power of 9 mEq./l. Following drainage of the carbuncle he was doing well until a few days later he suddenly developed hemiplegia and died.

Autopsy.—*Overgrowth of certain organs such as the heart (520 gm.), the liver (3800 gm.), the kidneys (the right 360 gm. and left 380 gm.) and the body generally. Atrophy or underdevelopment of the testes and the* prostate. A pituitary tumor of the chromaffin type compressed the hypothalamus and the anterior pituitary which was not destroyed. The absence of acidophilic granules while favoring a chromophobe tumor nevertheless does not rule out the possibility of an actively functioning tumor in the past. The hypothalamus was not destroyed but pressure upon the hypothalamus may have explained, in part at least, the insulin resistance. An area of grossly visible cystic softening was present in the left cerebral peduncle.

The tumor measured 4 cm. in greatest diameter and weighed 25 gm. It was composed of polyhedral cells, contained no eosinophilic or basophilic granules. These cells showed no mitotic activity. Many areas of necrosis and thrombosis of vessels were seen. The cells *were arranged in cords and masses, especially about blood vessels.*

The pancreas weighed 100 gm. and the large islets appeared hyperplastic.

Simultaneous *development of classic* Cushing's syndrome and acromegaly as described by Uhl and Pearson[157] *with metabolic studies by* Mc-

[156] Williams, P. 75, loc. cit., p. 619.
[158] Pfeiffer: German Medical Monthly, 5, No. 9, 278, 1938.
[157] Uhl and Pearson: Jour. Clin. Endocrinology, 11, 913, 1951.

Cormick, *et al.*[18] A forty-three-year-old negro woman had developed, since the age of thirty-four, amenorrhea, hypertension, generalized weakness, increased facial hair, loss of scalp hair, increased fat around the face, neck and abdomen, increased glove and shoe sizes, a weight gain of about 50 pounds, mild diabetes controlled with 25 units of protamine zinc insulin per day, and finally blurred vision with restriction of the lateral visual fields. She showed the typical "moon facies," hypertension, striæ over the buttocks and hips *together with bitemporal hemianopsia* *Following* craniotomy and partial removal of an adenoma she died six weeks after the first operation. Autopsy showed an eosinophilic adenoma replacing the anterior pituitary in which a preponderance of eosinophilic tumor cells with an admixture of abundant chromophobe cells and a few basophils were noted. The adrenals weighed 26 gm. Moderate osteoporosis of the spine was present.

During the period of metabolism studies the serum phosphorus levels were low. *After ACTH administration an increase in nitrogen loss occurred.* With an increase in dosage a further increase in nitrogen loss to 7 3 gm. was observed.

[illegible]

ride and metabolic alkalosis have been encountered frequently in patients with overactive adrenal cortical states Data suggested that administration of potassium may result in slight reductions of hyperglycemia and glycosuria Potassium deficiency may be related to impairment of glucose metabolism

From the Mayo Clinic Wilder[19] reported 20 cases of acromegaly among 9377 diabetics He pointed out that these 20 instances of diabetes occurred in 218 cases of acromegaly and included 13 frank cases of diabetes, an incidence of only 6 per cent The thyroid was adenomatous in one-half the cases and in some the diabetes preceded the acromegaly. He stated [illegible] in the production of [illegible] ncurred in recently by [illegible] [21] by Houssay and [illegible] in dogs could be [illegible] on which became the basis for much experimental work, has also been observed in man in at least 17 documented cases according to Calvert and Caplin [21] The pathologic lesions have been diverse, including infarction, tumor and abscess

Isolated impairment of the capacity of the anterior lobe to make one hormone or a group of hormones leaving the remainder of it's function intact, probably occurs, but is not often described. With decreased secretion of hormones the tolerance for carbohydrates rises, the insulin requirement falls rapidly, and severe insulin reaction may occur

Necrosis of the pituitary has occurred in association with such conditions

[18] McCormick, Reed, Murray and Ray: Am Jour Med , *10*, 662, 1951
[19] Wilder P 263-264, loc cit , p 71
[20] McCullagh, Beck and Schaffenburg Diabetes *4*, 13, 1955

as sarcoid, tuberculosis, and carcinoma in a wide variety of patients. In the case of Calvert and Caplin, a clergyman, age 76 years, became stuporous following prostatectomy, although he had required insulin with a blood sugar of 358 mg. Within a few days no insulin was required. Post-mortem examination showed, in addition to carcinoma of the prostate, necrosis of the pituitary.

Postpartum necrosis, often referred to as the Sheehan syndrome has been reported frequently in non-diabetics. Cases are described by Clark, Franklin and Sahs[22] in a woman with hypoglycemic convulsions and another by Williams[23] in which the diabetes almost disappeared. Spontaneous hypoglycemia occurred with death. Post-mortem examination revealed the evidence of an old hemorrhage and destruction of the pituitary.

In our Case, 8999, a young woman with juvenile type diabetes (onset age 14) following spontaneous stillbirth in the 29th week of pregnancy, insulin dosage fell from 100 to 120 units daily to zero in a period of two days, with a blood sugar of 14 mg. per cent on one occasion. Constant intravenous dextrose was required for 3 days in order to maintain safe blood sugar levels. Subsequently she has been well-regulated with 25 mg. of cortisone and 6 to 8 units of NPH insulin daily. Two particularly interesting features may be mentioned: (1) mild diabetes insipidus appearing during the initial therapy with larger doses of cortisone, and (2) return of vaginal bleeding resembling menses on four occasions in the past two years. Other patients with Sheehan's syndrome have had irregular, scanty menstruation or become pregnant[24] despite pituitary necrosis with practically no pituitary tissue demonstrable at autopsy.

We have observed one case of pituitary myxedema in which the diabetes disappeared. Hypopituitarism occurred in Case 22753, a bookkeeper, forty-seven years of age in 1943, with diabetes of 11 years' duration who entered the hospital because of hypoglycemic attacks. Her speech was slow, words were slurred, her movements were slow, the basal metabolism was minus 36 per cent. X-ray of the skull showed a great increase in size and depth of the fossa together with marked pitting of the posterior clinoids. Marked cortical atrophy was disclosed by air injections. With newer techniques for determining follicle-stimulating hormones of the pituitary (FSH), and ketosteroid excretion, partial failure of the anterior lobe to make one or more hormones will be found more frequently in patients with diabetes.

It is rare for patients with known hypopituitarism to develop diabetes. Such a case is described by Grunberg and Blair.[25] The patient, age 45, when first examined was sexually underdeveloped and incapable of coitus. Testes were small and face and body were hairless. X-ray examination of the skull showed the pituitary fossa normal and the spine showed generalized osteoporosis. There was 17-Ketosteroid excretion, 2 mg. a day. Glucose tolerance test was normal. He was given testosterone.

He returned in May, 1955, with the classical symptoms of diabetes mellitus. The blood sugar two hours after breakfast was 480 mg. Under

[21] Calvert and Caplin: Brit. Med. Jour., *2*, 71, 1957.
[22] Clark, Franklin, Murray and Sahs: Arch. Neurol. and Psychiat., *65*, 724, 1951.
[23] Williams: Diabetes, *1*, 37, 1952.
[24] Fajans: Jour. Clin. Endocrin. and Metab., *18*, 271, 1958.
[25] Grunberg and Blair: Brit. Med. Jour., *2*, 439, 1957.

treatment with insulin, within a few weeks, he began to develop attacks of hypoglycemia and on one occasion was admitted to the hospital in severe hypoglycemia requiring, not one, but repeated injections of 50 per cent dextrose. The results of radio-iodine tracer studies showed thyroid function to be almost negligible. Treatment consisted of a regime of

hair had not appeared.

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decrease in formation of new vessels was observed in 5 cases, and in one case, some newly-formed vessels disappeared and proliferation had diminished The first patient was operated on in 1951, and 11 had been operated on in July 1954. Since operation, 7 patients have died Substitution therapy after the first post-operative period included the administration of thyroid hormone, insulin, estrogenic hormone and adrenal cortical hormone The insulin for daily maintenance varied from 8 to 24 units In the surviving cases the operation was followed by a fall in blood pressure and decrease in heart volume No retinal changes had occurred in the limited period of observation

In reporting four cases of severe diabetes with progressive vascular disease who were subjected to hypophysectomy, Kinsell[27] emphasized the complicated nature of post-operative treatment with particular respect to *hormonal medication, and the necessity of reducing greatly the insulin* administration depending on frequent urinary tests and the management of electrolyte balance The marked insulin hypersensitivity could be balanced by the judicious use of cortisone or hydrocortisone One of their *four patients died of renal and cardiac failure five months after operation*

operation

At present

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Bilateral adrenalectomy has been employed as a means of stabilizing brittle, or unstabilized diabetes with the hope of controlling blood pressure Wortham and Headstream[28] subjected 7 patients with retinopathy of the severe type to this procedure In two patients, observed for 14 and 10 months respectively, some remission of vascular change was shown by minor reversals in retinal changes of all blood pressure, and decrease in proteinuria and nitrogen retention Three died within a few months

A twenty-eight year old housewife, with advanced intercapillary glomerulosclerosis, was subjected to adrenalectomy and a detailed study of *the chemical features post-operatively was reported by* Martin and

[26] Luft, Olivecrona, Ikkos, Kornerup and Ljunggren Ibid, *2*, 752, 1955, Javid, Gordon and Erickson Jour Neurosurg, *15*, 504, 1958
[27] Kinsell, Lawrence, Balch, Weyand Diabetes, *3*, 358, 1954
[28] Wortham and Headstream Ibid, 367, 1954

Wilson[29] She was maintained on 25–50 mg of cortisone orally per day with infrequent small doses of desoxycorticosterone. Death occurred from *adrenal insufficiency with hyperkalemia and ascending muscular paralysis* when the cortisone dosage was reduced from 50 to 25 mg per day in order *to relieve the malignant hypertension that had developed*

B THE THYROID AND DIABETES

General Considerations —The thyroid gland is related to diabetes by virtue of variations in levels of circulating thyroid hormone These levels are under the influence of (1) thyrotropic hormone (TSH) from the anterior pituitary, (2) the rate of utilization of thyroid hormone by body tissues, and (3) the amount of iodine available The pituitary thyroid axis normally presents a self-regulating, hormonal balance comparable to that between the pituitary on one hand and the gonads or adrenal cortex on the other[30] TSH, a glycoprotein of low molecular weight (≈ *10,000*),[31] exerts no effect on diabetes other than that produced by alterations in thyroid function *The presence or absence of diabetes seems not to alter these pituitary-thyroid relationships* Existence of a separate exophthalmos-producing *substance closely associated with thyrotropin has recently been postulated*[32]

Activity of circulating thyroid hormone was until recently attributed chiefly to l-thyroxine (tetra-iodothyronine), but the important role of l-triiodothyronine has been clearly demonstrated by Gross and Pitt-Rivers,[33] and Roche *et al*[34] This new hormone is much more active than l-thyroxine and may well be the true thyroid hormone The l-forms are ten to fifteen times as active as are the d-forms

In general, these substances aid in regulating the rate of metabolism, growth, and development of tissues Probably all body cells are affected *Their effects in the diabetic and on carbohydrate metabolism are a natural* result of such general metabolic actions The degree is usually, but not always, in direct proportion to the extent of alteration of metabolic rate, whether it be elevation (as in thyrotoxicosis) or depression (myxedema) Such relationships for diabetes and thyrotoxicosis have been summarized by Duncan[35]

Experimental Studies.—Ample experimental evidence indicates that hyperthyroidism aggravates and hypothyroidism may ameliorate certain defects in carbohydrate metabolism Thyroidectomy in normal animals increases the tolerance for carbohydrate and may even result in hypoglycemia[36] The administration of Thyroid Extract increases the discharge *of glucose from the liver* After thyroidectomy, hypoglycemic convulsions may occur with only a fraction of the insulin dose previously

[29] Martin and Wilson Ibid , 375, 1954
[30] Means Bull Johns Hopkins Hosp , 89, 90 106, 1951
[31] White Quoted by Williams Textbook of Endocrinology, Philadelphia, W B Saunders Co , p 38 1950
[32] Dobyns and Wilson Jour Clin Endocrin and Metab , 14, 1393, 1954
[33] Gross and Pitt-Rivers Lancet 1, 439, 593, 1952
[34] Roche Lissitzky and Michel Compt rend Acad d sci , 225, 1223, 1952
[35] Duncan 'Diabetes Mellitus,' Philadelphia, W B Saunders Co , p 8, 1951
[36] Britton Am Jour Physiol , 84, 133, 1928

necessary, before operation[37–38] Thyroidectomy or Thiouracil feeding may delay the onset of diabetes in pancreatectomized rats.[39] Diabetic animals *may show relative insulin insufficiency with exacerbation of diabetic symptoms as a result of the feeding of Thyroid Extract.*[40] In normal animals the administration of Thyroid Extract does not produce diabetes After [illegible]

[illegible]

appear but may disappear with cessation of Thyroid feeding. Houssay terms this reversible stage "Thyroid Diabetes." If, however, Thyroid Extract is administered for many weeks, the islet lesions may become irreversible and the diabetes permanent. Degeneration of the beta-cells occurs.[41–43] This he calls "Metathyroid Diabetes."

TABLE 117.—ALTERATIONS IN FUNCTION OF THE THYROID GLAND AND DIABETES

	Thyrotoxicosis	*Control of Thyrotoxicosis*
Diabetes	Aggravated	Ameliorated
Blood Sugar	Readily elevated	More stable
Glycosuria	Aggravated	Tends to be corrected
Absorption of sugar from intestines	Rapid	Depressed
Glycogen — Hepatic	Reduced	Normal or slightly decreased
Glycogen — Muscle	Reduced	Normal or slightly decreased
Protein catabolism	Increased	Normal
Gluconeogenesis	Stimulated	Normal
Need for insulin	Increased	Reduced
Duration of insulin action	Reduced	Prolonged

In opposition to these effects is the frequently observed stimulation of growth of islet cells in animals after prolonged feeding of Thyroid Extract. Indeed this observation has been the basis for attempts to stimulate islet cells in juvenile diabetics (Chapter 27)

Several mechanisms by which thyroid hormone may alter carbohydrate metabolism have been suggested, as follows: (1) An adrenergic-like action interfering with the storage of glycogen or increasing the release of glycogen from the liver as glucose[44] (2) Accelerated peripheral utilization of carbohydrate due to the general increase in metabolism[45] (3) Increased rate of absorption of glucose from the intestinal tract.[46] (4) Damage to the liver on occasions may be severe in hyperthyroidism[47] (5) Disturbed release of

[37] Burn and M[illegible] 131, 1935
[38] Bodansky [illegible] Progress in [illegible]
[illegible] ,8, 1944
[illegible] 187, 1946
[illegible] 36
[illegible] New York, The Blakis-
[illegible]

glucose from hepatic glycogen stores results.[48] (6) Adrenal atrophy with decline in secretion of corticosteroids to low levels following thyroidectomy might indirectly alter carbohydrate metabolism[49] (7) Exhaustion of beta-cell function with decreased endogenous insulin may occur in animals after partial pancreatectomy as a result of prolonged hyperthyroidism.[50] (8) The hereditary background of diabetes may be necessary in man if hyperthyroidism is to induce diabetes[51] Using insulin I^{131} in animals, Elgee and Williams[52] found that the chief sites of localization and presumably degradation of insulin I^{131} were the liver and kidney. The use of Thyroxin or Triiodothyronine increased the rate of deposit and change, whereas thyroidectomy diminished the rate.

In summary, since no single mechanism is completely satisfactory, it is reasonable to accept the interpretations of Barker[53] He has stated that Thyroxin increases the rate at which normal cellular chemical reactions occur Since no direct involvement of Thyroxin in an enzyme system has been demonstrated, he postulated that Thyroxin causes a release of coenzymes or other materials needed in the energy transforming processes in all cells

Morphologic changes in the pancreas characteristic for thyrotoxicosis have not been found, according to Warren and LeCompte[54] Although in alloxan diabetes of the rat,[55] changes in the thyroid suggesting hypofunction have been described, Warren and LeCompte have found no such lesions in the thyroid in diabetic patients[56]

Cell mapping of thyroid glands taken from a series of diabetics and compared with non-diabetic controls by Goddard and Sommers[57] disclosed only changes in type II cells, possibly related to increased blood sugar levels

Hyperthyroidism —The increased incidence of glycosuria accompanying diseases of the thyroid is fundamentally due to hyperthyroidism In 500 cases of thyroid disease from the Lahey Clinic series[58] the incidence of glycosuria in primary hyperthyroidism was 38 6 per cent, in adenomatous goitre with hyperthyroidism 27 7 per cent, in non-toxic goitre 14 8 per cent, and in a large control sample 13 6 per cent Clinical diabetes was present in 2 5 per cent of those with primary hyperthyroidism and 4 3 per cent of those having adenomatous goitre with hyperthyroidism (See Table 118)

a Incidence of Diabetes in Hyperthyroid Patients In patients with potential diabetes thyrotoxicosis has been shown by Wilder[59] to produce an earlier appearance of diabetes On the other hand, his reported incidence of 1 3 per cent diabetes in a large series of Mayo Clinic patients with

[48] Ibid p 31
[49] Evans, Simpson, and Pencharz Endocrinology, 25, 175, 1939
[50] Rogers and de Fuss Jour Amer Med Assn, 123, 50, 1943
[51] Ricketts In, Progress in Clin Endor, ed by Soskin, Section VI, Chapter 2, New York Grune and Stratton, 1950
[52] Elgee and Williams Diabetes, 4, 87, 1955
[53] Barker Physiol Rev, 31, 205 1951
[54] Warren and LeCompte Pathology of Diabetes Mellitus, '4th Ed, Lea & Febiger, Philadelphia To be published
[55] Applegarth and Koneff Anat Rec, 96, 13, 1946
[56] Warren and LeCompte Loc cit, p 629
[57] Goddard and Sommers Diabetes, 3, 383, 1954
[58] Joslin and Lahey Amer Jour Med Sci, 176, 1, 1928
[59] Wilder Loc cit p 71

hyperthyroidism, 1935–1938,[60] although three times greater than the incidence 10 years earlier, is far less than the 17 per cent incidence of diabetes found among acromegalics by Coggeshall and Root.[61] Wilder wisely attributed this increase in diabetes to the mounting diabetic morbidity in the population.

Reports of diabetes occurring with hyperthyroidism (see Table 118) have shown a distinct overall increase to from 2 to 3 3 per cent. However, this occurred chiefly in patients having adenomatous goitre with hyperthyroidism, which appears characteristically at an age when the onset of diabetes is most common.

Hyperthyroidism accompanying diabetes has frequently been reported to be relieved by the use of propylthiouracil, as illustrated by the reports of DeCastro and Teixera [62]

ated and accelerated the downward course of the other [63]

Disaster is imminent when uncontrolled diabetes (ketoacidosis and coma) and hyperthyroidism ("thyroid storm") occur together Six patients, Cases 4306, 5346, 13172, 4289, 9365, survived coma with hyperthyroidism through January, 1951, and five others, Cases 24821, 38820, 38920, 41950, 44873, have recovered in the most recent series ending September, 1957 [64] One patient, Case 4306, was diagnosed as diabetic when in coma, and another, Case 13172, had both coma and "thyroid storm" simultaneously [65]

Ketoacidosis and coma may develop with unusual rapidity in the hyperthyroid diabetic Early diagnosis and intensive treatment with insulin and fluids are essential, as indicated by our previous experience and especially well-described by Troen, Taymor and Goldberg[66] who treated a 49 year old woman in coma and thyroid crisis, giving 350 units of insulin and 6000 cc fluid intravenously in the first six hours On recovery her basal metabolism was +73 per cent and the cholesterol 102 mg. per cent.

On occasions hyperthyroidism has been diagnosed so early that many usually reliable clinical features are missing Suspicion is raised by changes in the diabetic state, such as unexplained increase in insulin requirement, instability of diabetes, recurring ketosis, nausea and vomiting. At such times results of laboratory tests for hyperthyroidism may be normal or show a borderline elevation Diagnosis is confirmed only when distinct response to treatment is shown

In the current series (1951–195
11 showed thyrocardiac disease w
heart failure, or both, as the chief

[60] Wilder Loc cit p 71
[61] Coggeshall and Root Loc cit , p 620
[62] DeCastro and Teixera Medicina-cirurgica-farmacia, *190–191*, 67, 1952
[63] Joslin and Lahey Loc cit p 629
[64] Ferguson and Bradley To be Published
[65] Root Medical Papers Dedicated to Henry A Christian, Baltimore, Williams and Wilkins, p 434, 1936
[66] Troen, Taymor and Goldberg New England Jour Med , *244*, 391, 1951

these, Cases 37345, 21122, 38626, required digitalis after hyperthyroidism had been corrected One died before the euthyroid state was reached. All of these persons were in the older age groups, with coronary heart disease as the underlying factor

In most instances, the diabetic behaves in the same manner as the non-diabetic, whether the diagnosis is primary hyperthyroidism (Graves' disease) or adenomatous goiter with secondary hyperthyroidism

TABLE 118 —INCIDENCE OF DIABETES MELLITUS WITH HYPERTHYROIDISM PER CENT

		HYPERTHYROIDISM		
SOURCE	NORMAL	*Primary*	*With Adenomatous Goiter*	*All Cases*
Surveys[47]	1 7			
Mayo Clinic[48]	1 7	1 7	5 6	3 3
Lahey Clinic[49]		2 5	4 3	3 2
John[50]				2 3
Lahey Clinic—1947[71]				2 0

Formerly, the dire emergencies of diabetic coma or thyroid crises were natural sequelæ to hyperthyroidism complicating diabetes, now the clinical picture has changed because of early diagnosis and use of potent antithyroid drugs

(c) *Incidence of Hyperthyroidism in Diabetics* —In a series of 42,800 true diabetics seen at the Joslin Clinic between 1928 and September 30, [illegible]

most recent series, January 1, 1951 through September 30, 1957, among 18,439 diabetic admissions to the New England Deaconess Hospital, 86 hyperthyroid cases occurred, an incidence of 0 5 per cent Correcting for readmissions, the incidence for hyperthyroidism in 11,985 diabetics was 0 7 per cent Data for the surgical series are presented in Table 121

[illegible] —If either [illegible] significant [illegible] ducing the other At one time it appeared the exact onset of diabetes was more easily determined, but its insidious appearance, especially in adults, with long intervals when symptoms may be absent or minimal, has made definite timing difficult

The earlier series of diabetics from predominantly surgical clinics indicated the prior appearance of primary hyperthyroidism in 75 to 85 per cent of patients and of adenomatous goitre with secondary hyperthyroidism in 47 to 62 per cent Regan and Wilder[72] reported 52 per cent prior appearance for diabetes and 62 per cent in cases of adenoma with secondary

[47] See Chapter 2, p 35
[48] Wilder *Loc cit* p 71
[49] Joslin and Lahey *Loc cit* p 629
[50] John Jour Clin Endocrin, 2, 264, 1942
[71] Allen Lahey and Murphy Trans Am Assn for Study of Goitre, p 248, 1947
[72] Regan and Wilder Arch. Int Med, 65, 1116, 1940

hyperthyroidism. A more recent Lahey Clinic series[73] revealed primary hyperthyroidism before diabetes in 54 per cent of their cases and the prior onset of goitre with hyperthyroidism in 68 per cent.

More significant figures are derived from results in diabetics developing hyperthyroidism Bowen and Lenzner[74] report the earlier appearance of diabetes in the "majority." Our current series [75] reveals that only 6 out of the 86 with hyperthyroidism developed hyperthyroidism first. This was of the primary type.
66 per cent and adenomato
Simultaneous onset was rec
a 55 per cent heredity for diabetics with primary hyperthyroidism and 40 per cent for those having adenomatous goitre with secondary hyperthyroidism. Our earlier series revealed diabetic heredity in 52 per cent, while in the current series it is 42 per cent, not including two patients with uncertain history.

(e) *The Diagnosis of Diabetes in Hyperthyroidism*—Hyperthyroidism accentuates the disturbed carbohydrate metabolism of the diabetic, and experimental evidence indicates that several mechanisms may contribute to this condition. Also, 1½ to 2 times as many people, without known diabetes, develop hyperglycemia, or glycosuria or both in association with hyperthyroidism as would be expected in its absence. Some of the latter may show varying degrees of restoration of carbohydrate metabolism toward normal levels after treatment of hyperthyroidism. Although occasional case
after treat
not occurre
aline in hy
glycosuria.
ar
on
by hyperthyroidism. However, if diabetes is considered as an hereditary disorder characterized by predisposition of the islet cells to injury and the only demonstrable evidences of such islet cell failure are changes in carbohydrate metabolism, then hyperthyroidism has not provoked diabetes, but merely chosen the time when endogenous insulin production failed sufficiently to be detected. Significant incidence of diabetic heredity where hyperglycemia and glycosuria followed hyperthyroidism would strongly support the latter concept

Postprandial hyperglycemia and glycosuria may occur as a result of increased glucose absorption with hyperthyroidism This might account for at least a portion of the inordinately high incidence of glycosuria in non-diabetic persons Perhaps the standards for normal by glucose tolerance test would need to be altered, but the phenomenon of increased absorption should not affect the fasting levels or those taken two to three hours after a glucose load if endogenous insulin is adequate

[73] Allan, Lahey and Murphy Loc cit p 630
[74] Bowen and Lenzner New England Jour, 245, 629, 1951
[75] Ferguson and Bradley Loc cit p 630, Diller and Kilpatrick Brit. Med Jour, 2, 823, 1958

In making a diagnosis of diabetes when hyperthyroidism is present, extreme caution must be used

Since slight abnormalities of carbohydrate metabolism may disappear with treatment of hyperthyroidism, one must avoid a diagnosis of diabetes and an assumption that a cure has been achieved It was formerly the custom to alter criteria for diagnostic blood sugars by arbitrarily raising the levels (Folin-Wu method on venous blood) from 130 to 150 mg. per cent fasting and from 170 to 200 mg. per cent postprandially, in addition to glycosuria If these criteria are to be used and "True" blood sugars (Somogyi-Nelson) on venous blood are being determined, then each of the diagnostic levels would be reduced by 20 mg per cent to 130 and 180 mg per cent

No attempt should be made for a definite diagnosis of diabetes in patients with hyperthyroidism when only slight alterations in carbohydrate metabolism are found Re-evaluation is desirable, after the patient has recovered from hyperthyroidism, using postprandial blood sugars or glucose tolerance tests with standard criteria (see Chapter 8)

If we accept the concept that hyperthyroidism alone rarely produces diabetes then any abnormality of carbohydrate metabolism seen while hyperthyroidism is present means diabetes, with two possible exceptions (*a*) glycosuria without hyperglycemia or, (*b*) transient hyperglycemia occurring within two hours postprandially or following a glucose load (to allow for supernormal absorption)

Hyperglycemia and glycosuria persisting when a patient has become euthyroid always denote diabetes unless some other condition is present that could profoundly interfere with utilization of glucose

Hyperglycemia and glycosuria of sufficient severity to require insulin or produce ketoacidosis almost invariably indicate diabetes regardless of the severity or duration of hyperthyroidism

TABLE 119 PRIOR ONSET OF DIABETES OR HYPERTHYROIDISM
(Jan 1, 1951—Oct 1, 1957)
Experience of Joslin Clinic in 86 Patients

Appearing Earlier	*Primary Hyperthyroidism*	*Adenomatous Goiter with Hyperthyroidism*
Hyperthyroidism	5	1
Diabetes	36	21
"Simultaneous"	14	9

(*f*) *Age* In our series, bilateral subtotal thyroidectomy for primary hyperthyroidism was done six years later than the average age for the onset of diabetes In diabetics with adenomatous goitre and secondary hyperthyroidism the operation was performed 11 years after the date of onset of diabetes (see Table 121) In general, primary hyperthyroidism is occurring and being treated 15 to 20 years earlier in the diabetic than is adenomatous goitre with hyperthyroidism The age range in those diabetics with primary hyperthyroidism was from 16 to 65 Adenomatous goitre with hyperthyroidism was found at ages 21 to 71

(g) *Sex.*—Female diabetics predominate overwhelmingly. In the last series, of the 54 patients with primary hyperthyroidism 40, or 79 per cent, were women Among 32 patients with adenomatous goitre and hyperthyroidism, 28 were women.

(h) *Diagnosis of Hyperthyroidism.*—The presence of hyperthyroidism should be suspected in diabetic patients with or without thyroid enlargement in the presence of unexplained weight loss, supraventricular tachycardia, increased body warmth and tremor, or unexplained increase in insulin requirement, ketoacidosis or instability of the diabetes. In several

He had no palpable goitre, but abrupt increase in severity of his diabetes and unexplained arrhythmia led to the diagnosis after recovery from coma.

(i) *Basal Metabolism.*—The basal metabolic rate continues to be our most commonly used procedure for diagnosis of hyperthyroidism in diabetic patients for two reasons: (1) it is cheaper, and (2) it is an accurate test when done under proper conditions. Falsely elevated readings are the most difficult problem Errors in diagnosis may be reduced by several expedients. The presence [illegible] basal metabolic rates below [illegible]

Sedation [illegible]

bolic rates in the range of [illegible] test under sodium pentotl[illegible] been outlined by Bartels.[76] [illegible] and without sedation became zero under anesthesia and the amount of sodium pentothal needed to produce anesthesia was in the lower dosage [illegible]

ation

Determinations of protein-bound iodine have been used increasingly in diabetic patients where the diagnosis remains questionable. The serum protein-bound iodine has been of special value in older hyperthyroid diabetics with nodular goitres and in detecting low thyroid function following thyroidectomy [illegible] Bell.[77]

One elderly [illegible] ree years was diagnosed by a [illegible] per cent. The basal metabolic rate was +8 per cent, and her only symptom was weight loss A partially substernal goitre had been present for many years

Although normal euthyroid patients have remarkably constant serum protein-bound iodine levels, the commonly accepted range of 4 to 8 gamma

[76] Bartels Jour Clin Endocrin, *9*, 1190, 1949
[77] Bell Postgrad Med, *21*, 456, 1957

per cent
limit of 8
7 7 gamm

bec
me
(Graves's disease) but may
occurring in nodular goite , uptakes may
require repetition after a brief course of antithyroid treatment if diagnosis
is uncertain

... cases in non-diabetic as well as
diabetic patients without clear explanation The older
diabetic
in the pre
still eleva

TABLE 120 —HYPERTHYROIDISM AND CARCINOMA OF THYROID IN 32,229 CASES OF TRUE DIABETES MELLITUS

1928—January 1, 1951

	No Cases	Cases Operated	Sex Male	Sex Female	Ave Age Onset of Diabetes	Ave Age at Operation
Primary hyperthyroidism	234	195	66	168	41	44
Adenomatous goitre with hyperthyroidism	181	165	28	153	50	55
Carcinoma	3	3	1	2		
Total	418	363	95	323		

Formerly, all our diabetics with hyperthyroidism were prepared for surgical removal of the thyroid During the last five years an increasing number have been treated with radioactive iodine However, the greatest number continue to be made euthyroid by antithyroid drugs, with subsequent bilateral subtotal thyroidectomy, (see Table 121)

One cogent argument for thyroidectomy in the diabetic is his susceptibility to ketosis of severe degree under the influence of hyperthyroidism Therefore, he should receive the treatment
of or

Our
diabet
noted

(1) Preoperative Treatment Once the

... is made whether to use thyroidectomy or radioiodine, and the time is chosen for the procedure

[27] Blackburn and Power Trans Am Goitre Assn Meet, p 249, 1955

The diet frequently needs to be liberalized in order to correct the weight loss and debilitation that not infrequently occur with hyperthyroidism. Antithyroid therapy is prescribed.

TABLE 121.—THYROID CONDITIONS (EXCLUDING MYXEDEMA) IN 18,439 DIABETIC HOSPITAL ADMISSIONS

January 1, 1951—October 1, 1957

	No. Cases	Cases Operated	Sex		Ave. Age Onset of Diabetes	Ave. Age at Operation
			Male	Female		
Primary hyperthyroidism	54	37*	14	40	30	36
Adenomatous goitre with hyperthyroidism	32	18†	4	28	49	60
Adenomatous goitre without hyperthyroidism	327	23				
Chronic thyroiditis	4	1				
Hürthle cell adenoma (one with subacute thyroiditis)	3	3				
Fibrosarcoma	1	1				
Carcinoma	2	2				
Total	423	88				

* Bilateral subtotal thyroidectomy
† Bilateral subtotal thyroidectomy 13, Hemi-subtotal thyroidectomy 4, Excision of adenoma 1

Some cases of mild hyperthyroidism may be controlled by Lugol's solution, 10 drops daily, or a standard solution of potassium iodide. These

I

the last 6 years, 5 diabetic patients, all with primary hyperthyroidism,

wi

sur

response to thiourea derivatives. The purpose of iodide therapy is to give the surgeon at operation as firm and avascular a gland as is possible. It is unnecessary for adenomatous goiters with hyperthyroidism.

Because of its toxicity, Thiouracil is no longer used. Methylthiouracil has been discarded for the same reason. Tapazole (methimazole), though less toxic than Thiouracil and Methylthiouracil, has produced more side

[77] Bartels: Ann. Int. Med., 37, 1123, 1952.

with the degree of elevation of a reliable basal metabolism and the size of the goiter, as follows

(1) primary hyperthyroidism—one day of treatment with Propylthiouracil for each point elevation of the basal metabolism.
(2) adenomatous goiter with hyperthyroidism—two days of treatment with Propylthiouracil for each point elevation of the basal metabolism
(3) daily dose—100-150 mg Propylthiouracil every 12 hours for hyperthyroid subjects having small goiters This lower dosage range would usually apply to those having primary hyperthyroidism
(4) Propylthiouracil 200-300 mg every 12 hours for those with moderate to large size goiters Usually applicable to those having adenomatous goiter with hyperthyroidism

On the advice of Bartels[40] higher dosages, 300-500 gm every 12 hours, have been used, and have effected more rapid subsidence of the hyperthyroidism, thus shortening the period during which a patient needs to be under observation and decreasing the length of time for exposure to the potential side effects of the drug Reactions to Propylthiouracil are idiosyncratic in nature and not dose related No increased incidence of toxicity has been noted

The goal in antithyroid treatment is to reach a point at the time of surgery where symptomatic improvement has occurred, previous weight loss has been at least partially corrected, resting pulse has returned to normal, and the basal metabolism is +10 per cent or less However, significant hypometabolism or clinical myxedema should be avoided, as edematous tissues in the neck make surgery difficult and increase the risk of laryngeal edema

Additional measures for correcting hypermetabolism are (1) avoidance of undue excitement, fatigue or strain, (2) sleeping a minimum of 8 to 10 hours nightly, (3) avoidance of stimulants such as coffee, tea or cocoa, with preferably the omission of smoking and alcohol, and (4) the omission of iodine-containing medicines or vitamins containing iodine

All patients are instructed to report promptly the occurence of fever, sore throat or rash Periodic white blood counts are unnecessary, but should be done as a baseline before antithyroid treatment and immediately if any of the above symptoms occur

Sudden variations in carbohydrate metabolism may take place in association with changing outputs of thyroid hormone At least two urine tests for sugar should be done each day, additional crystalline insulin given when indicated, and the physician notified at once when glycosuria persists

If weight has fallen as a result of hyperthyroidism, the diabetic diet must be *increased to assist in regaining it* *Carbohydrate may need to be* increased to as high as 200 or 250 grams per day, the protein to 1½ or even 2 grams per kilogram of ideal body weight, and sufficient fat to allow total intake of 30 to 35 calories per kilogram of ideal body weight On the other hand, many hyperthyroid diabetics, particularly those having adenomatous

[40] Bartels *Jour Clin Endocrin and Metab*, *11*, 1403, 1951

goiter [illegible]
weight [illegible]
weight [illegible]
tion is indicated.

Long-acting insulin should be continued and increased by 10 to 20 per cent every 3 to 4 days if urine tests are consistently poor. Supplementary crystalline insulin should be used in amounts of 10 to 20 per cent of the usual morning dosage, and should be administered before the noon and supper meals in accordance with the results of tests for sugar in the second voided urine, (see Chapter 9).

Except in cases with stable diabetes, strict control with insistence on sugar-free specimens is unwise Because of improvement under antithyroid treatment and reduction in metabolism, the daily insulin requirement may fall abruptly as the euthyroid state is approached. This increases the chance of severe insulin reaction.

(*k*) *Surgery* —In the current series[n] of 55 hyperthyroid diabetics prepared for surgery, 50 underwent bilateral subtotal thyroidectomy, 4 had subtotal thyroidectomy on one side, and 1 excision of an adenoma. No instance of "thyroid storm" has been recorded recently. Occasional [illegible]

cc. of 5 per cent dextrose in water or 5 per cent dextrose in saline. Saline is avoided in patients where myocardial failure may occur easily. Most patients have no oral intake of food or fluid during the first 24 hours. A few may take small amounts of water The usual totals are 2,000 cc. of water and 100 grams of dextrose intravenously Ideally, these fluids are administered at a rate delivering 10 to 15 gms of dextrose per hour.

Insulin dosage is managed in accordance with the general principles outlined on page 595 Long-acting insulin is not discontinued Most cases, whether operated upon for toxic or non-toxic goiter, tend to have more rather than less hyperglycemia and glycosuria

During the second 24 hour period, oral intake usually supplies about 50 per cent of the water and carbohydrate needs, the deficit being made up by 1,000 cc of water and 50 grams of dextrose intravenously. On subsequent post-operative days, diabetic patients may take sufficient fluid and food to make further parenteral feeding unnecessary.

Most diabetics are discharged on the fifth to seventh post-operative day with essentially the same insulin dose as was required pre-operatively. It is wise for them to be followed for a year at three month intervals Thyroid status is reviewed Uncomfortable symptoms of myxedema are treated with thyroid extract, or in some instances tri-iodothyronine On occasion the diabetes may require adjustment at more frequent intervals

Post-operative deaths amounted to 1.9 per cent of 308 diabetics having thyroid surgery prior to January, 1951 No deaths occurred for the years 1946-1951 From 1951 through September, 1957, one death, (Case 38725), occurred two hours after surgery Postmortem examination showed

n Ferguson and Bradley Loc cit, p 632

"acute cerebral edema." This was a 39 year old man with moderately long duration of diabetes and an old, antero-septal myocardial infarction. No cause for "cerebral edema" was found.

(*l*) *Results.*—No instance of a cure for diabetes has been observed among patients following a return to the euthyroid state. However, there are five, (Cases 48838, 44600, 39584, 41833, and 41888), *in whom gain in tolerance* has been shown to the point where all urine specimens are sugar-free and random blood sugars normal. At present all are being studied through glucose tolerance tests.

Follow-up of the current operated series for six months to 6½ years reveals: (1) with a few striking exceptions total insulin dosage has not materially changed, (2) recurrence or persistence of hyperthyroidism has been nil, (3) transient myxedema (during one year or less) appeared in 10 cases, while in 7 others myxedema has persisted after 2 to 5 years and requires thyroid treatment. (This 10 per cent of permanent myxedema is higher than the 5 to 7 per cent usually reported for subtotal thyroidectomy.)[32] (4) parathyroid deficiency with tetany has been temporary, (Case 34795), and appears (8 months after operation) to be permanent in one other, (Case 33760).

(*m*) *Medical Treatment of Hyperthyroidism.*—Thirty-one patients in the current study series (1951–1957) have received treatment other than thyroidectomy. This occurred because (1) the patient refused a planned thyroidectomy or was considered too poor a risk, (2) thyroidectomy was delayed and later performed elsewhere (Cases 47364, 39967), (3) hyperthyroidism was mild, subsiding promptly and completely with Lugol's solution, (4) treatment with radioactive I^{131} was elected (10 diabetics).

Thiourea derivatives, chiefly Propylthiouracil, are being used in our diabetic patients only in preparation for thyroidectomy or radioiodine. Their long-term use in the control of hyperthyroidism, although popular and used with considerable success in some thyroid clinics, has not seemed advisable for the diabetic whose hyperthyroidism should be removed with the least possible chance for either persistence or recurrence. The debilitated, elderly thyrocardiac, although not the ideal candidate for thyroidectomy, or with a nodular goiter that would be difficult to treat with radioiodine, is given propylthiouracil with the expectation that eventually thyroidectomy may be performed with little risk. Individuals in this category together with others illustrated by Case 49912, a 10-year old boy with primary hyperthyroidism make up a group of diabetics receiving only antithyroid drug therapy.

Of the ten diabetics, age 51 to 72, who received radioiodine, eight had primary hyperthyroidism. Two having adenomatous goiter with hyperthyroidism were considered poor risks for surgery. The Cancer Research Institute of the New England Deaconess Hospital has supplied the isotope. Its use in diabetic patients has been under the guidance of Drs. Elmer Bartels and George Bell of the Lahey Clinic. Indications for radioiodine are: (1) patients with recurrent hyperthyroidism, and (2) patients over 40 years of age with primary hyperthyroidism.

[32] Bartels. Jour. Clin. Endocrin. and Metab., 13, 95, 1953.

Because medical thyroidectomy produced by radioiodine takes many weeks, the need to control hyperthyroidism more quickly in diabetics is met ... fore administration of ra ... days before radioiodin ... eeks, until destruction of thyroid tissue by the isotope has proceeded far enough to prevent recurrence of ... is is shown in Figure 28 ... "storm" due to disruptio

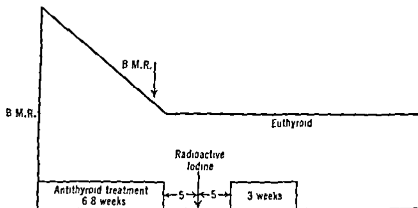


Fig 28.—Method of using antithyroid treatment in patients with moderate and severe hyperthyroidism in preparation for treatment with radioiodine.

In those with mild hyperthyroidism, prior treatment with Propylthiouracil or other antithyroid agents may be unnecessary, as the time delay, before radioactive iodine is effective in controlling the hyperthyroidism, may not be harmful

The dose of radioiodine has usually been calculated on the basis of estimated weight of thyroid tissue, 150 to 200 microcuries per gram. Diabetics have received from 4 to 8 millicuries Emphasis has been slightly on the side of overtreatment in an effort to avoid the effects of persisting hyperthyroidism in the diabetic and also the additional cost of subsequent repeat therapeutic radioiodine

Although Bartels, Bell and Zellman[33] found a 20 per cent incidence of

... less than 5 per cent, or essenti- ... Thus, a cure-rate compar- ... btained in primary hyper- ... risk a higher incidence of permanent myxedema

[33] Bartels, Bell and Zellman Lahey Clinic Bulletin, 10, 135, 1957

mean that multiple doses of radioiodine will frequently be necessary and the

F

Of

exc

admissions in this period. Eliminating the re-admissions, about one-third, an approximate figure of goiter incidence would be 3 4 per cent Women predominated

The incidence of goiter in diabetics varies considerably according to the region from which they come but undoubtedly is present much more fre-

Skouby[64] in Denmark found goiter in 10 per cent of women and 1 per cent of men with diabetes In diabetics followed for a number of years, Ralli and others[65] discovered enlarged thyroids in 17 per cent, indicating the increasing incidence of goiter in diabetics under long-continued observation and study

Spontaneous myxedema accompanying diabetes mellitus is uncommon In an effort to ameliorate diabetes, myxedema has been produced through

betics" excluding glycosurics were recorded[69] One woman has been eliminated from the original series because her myxedema occurred post-operatively, (Case 20132) The series of 15 cases is summarized in Table 122.

There are 12 females and 3 males Five of the females were juveniles, of whom three showed features of juvenile myxedema intermediate between those of cretinism and adult myxedema These three had diabetic coma prior to treatment with thyroid A fourth, age 31, after 21 years of diabetes, is well and has had three successful pregnancies Her only evidence of

heart was questionable in one woman, but was definite in one young man

[64] Skouby Acta Med Scand, 155, 401, 1956
[65] Ralli, Street and Pell Diabetes, 4, 456, 1955
[66] O'Day New York Med Jour, 105, 353, 1913
[67] Wilder, Foster and Pemberton Endocrinology, 18, 455, 1934
[68] Rudy, Blumgart and Berlin Am Jour Med Sci, 190, 51, 1935
[69] Joslin et al Loc cit, p 416

TABLE 122 —MYXEDEMA AND DIABETES IN 15 PATIENTS

October 1, 1957

Case	Sex	Age at Onset		Cholesterol mg Per Cent	Basal Metabolism Per Cent	Treatment		Complications	Living Age Years	Dead Age Years	Cause
		Diabetes Years	Myxedema Years			Thyroid Grains	Insulin Units				
28866	F	48	−57	322	−21	1	20 + [40]	(?) Myxedema Heart age 59 Essential hypertension Pyelonephritis, (?) Nephrophy, Angina Pect	63		
37307	F	36	49	703	−37	1	[20]	A-V block (?) Angina	54		
19560	F	9	9 Actually preceeded D M	600	−40	1	16 + [24]	Coma 338 Units Cretinoid features, Dwarfism	25		
21762	M	21	30	232	−36	3	16 + [18]	Myxedema heart[a] Nephropathy Retinopathy Uremia	36		—
16787	F	36	−47	256	−30		2 + [40]	Infected foot Essential hypertension, Iritis, Nephropathy, Congest heart fail		51	(?) Arteriosclerosis Coronary
14850	F	10	12	451	−42	4	20 + [40]	Live babies[a] Minimal retinopathy	31		
10444	M	66	59	179	−25	1	24-0-24			73	Hypoglycemia or CVA

11362	M	58	61	250	−31	1	0			61	Congenital heart failure (?) due to myocard infarction
504235	F	13	−13	216	—	2	[10] [36]	Mongoloid, Diabetic Coma while myxedematous Anemia of hypothyroidism	13		
2899	F	55	53	—	−32	5	32-0-16	Essent hypertension. Bilate amputations for gangrene		70	Coronary occlusion
21367	F	10	15	1170	−69	2	4 + [4] to 70 + [70]	Cretinoid features, Dwarfism, probable rheumatic heart disease with A I Coma while myxedematous B S 600, CO_2 6		23	Sudden, (?) Coronary or due to R H D
22616	F	56	41	448		2-4	[204]	Toe amputation	760		
7251	F	14	35	174	−36 −6 with treatment	1	[16] [28] with treatment		38		
49126	F	68	68	251	−9	2	10 + [30]		69		
12713	F	55	67	214	−26	2	[16]		78		

[1] Protamine Zinc Insulin
[2] With myxedema, fasting blood sugar was 140 mg per cent while taking no insulin Now (1958) is on 8 + [20]
[3] Subject of case report by Dr J Lerman
[4] NPH Insulin
[5] Diagnosis confirmed by Serum Protein Bound Iodine of 0 9 gamma per cent and subsequent dramatic response to thyroid

whose case has been reported by Lerman.[90] Despite earlier requirements for 30 to 40 units of insulin daily, this man has presented persistently sugar-free urine and minimally [illegible] insulin, as frequently occurs d[illegible] With adequate thyroid therapy [illegible] diabetic and renal retinopathy, and within a few months after his stay at the Massachusetts General Hospital developed marked albuminuria, uremia and anemia. He now has typical features of far-advanced diabetic nephropathy. In retrospect, one may say that a factor contributing to his marked edema was alteration in renal function produced by diabetic nephropathy prior to the onset of persisting albuminuria.

Spontaneous hypothyroidism and diabetes mellitus have been reported in 52 patients including the 15 in our series and 37 from the summaries of Baron[91] and Rupp *et al.*[92] Of these, diabetes has appeared first in twenty, [illegible] *may be considered doubtful. Data is lacking as to the prior onset of diabetes* or myxedema in 9 of the 52 cases.

Hypothyroidism accompanying multiple hormonal defects and diabetes has been reported in a few instances.[93] One of these was due apparently to isolated deficit in thyrotropic hormone.[94, 95] In our experience, no occasion has arisen for the use of the thyrotropic hormone response test as an aid in the differential diagnosis of hypothyroidism.[96]

Although untreated myxedema may reduce the severity of diabetes and the insulin requirement, it does not preclude the occurrence of severe uncontrolled diabetes, ketoacidosis, and coma. Furthermore, adequate treatment of myxedema will lead to the reappearance of the same severity of the metabolic state seen prior to the onset of myxedema.

The two conditions are unrelated from an etiologic standpoint, except that treatment of myxedema with thyroid hormone may force into the open latent or asymptomatic diabetes. Diabetes and spontaneous myxedema occur together no less frequently than their independent frequencies warrant.[99]

The combination of diabetes and myxedema is uncommon in our experience although Lawrence[100] has seen 50 such cases. Such diagnoses may become more frequent because of the increased longevity of the diabetic, and the availability of serum protein bound iodine determinations which, under appropriate conditions, provide valuable aid in making the diagnosis of hypothyroidism.

[90] Lerman: Jour. Clin. Endocrinol. and Metab., 14, 177, 1954.
[91] Baron: Lancet, 2, 796, 1955.
[92] Rupp, DiGeorge and Paschkis: Diabetes, 4, 393, 1955.
[93] Schulman: Jour. Clin. Endocrinol. and Metab., 14, 795, 1954.
[94] LaLuente: Acta Endocrinol. (Kbh.), 6, 136, 1951.
[95] Bernstein: Jour. Clin. Endocrinol., 8, 682, 1948.
[96] Howard and Matthews: Ibid. 12, 871, 1952.
[97] Colquell and Parsons: Ibid. 14, 881, 1954.
[98] Quenda and Stanbury: Ibid. 10, 1192, 1950.
[99] Baron: Loc. cit. p. 811.
[100] Lawrence: The Diabetic Life, 15th ed., London, Churchill, 1955.

C. THE ADRENALS AND DIABETES

Clinical disorders involving either the adrenal medulla or the adrenal cortex have important relationships with diabetes * The role of the adrenal cortex in homeostasis is attested by the inability of the adrenalectomized animal or patient with Addison's disease to cope with the exigencies of the environment.[101] In the absence of the pituitary gland the adrenal cortex becomes inert. The number of pituitary trophins acting upon the adrenal is uncertain, but maintenance of structure, growth and secretory activity of the adrenal cortex are regulated by an anterior pituitary hormone, *adreno corticotrophin* (ACTH) [101a]

1. Adrenal Cortex

(*a*) **Addison's Disease.**—Bilateral destruction of the adrenal glands commonly produces insulin sensitivity and frequent hypoglycemic episodes [illegible]

and functional tests A level of circulating eosinophils less than 50 per mm. rules out Addison's disease, as does also a fall of more than 50 per cent in the eosinophil count at the end of four hours after intramuscular injection of 25 mg of ACTH The 48-hour ACTH test utilizes the response of the 17-ketosteroids excretion and the eosinophil after 10 mg ACTH are given every six hours, or a total of 80 mg The oral glucose tolerance test may give a flat curve because of delayed absorption of glucose The intra- [illegible] ycemia [illegible] ognized in this series [illegible] Case 22770, in June, [illegible] rs in 1943 In June, 1951, his chief complaint was drowsiness and lassitude The insulin re- [illegible]

Evidence of electrolyte imbalance consisted of low serum sodium and moderately elevated serum potassium The Kepler-Power water test was abnormal The eosinophils failed to respond to two adrenalin and one 25

* For access to the literature the bibliography of 3,447 articles entitled *The Pituitary-Adrenocortical Function* may be consulted Baer Spencer *et al* have emphasized particularly articles dealing with ACTH and Cortisone Diabetes is the subject of 38 articles

[101] Baer, Spencer *et al* The Pituitary-Adrenocortical Function, Army Medical Library, Washington D C Dec 1950

[101a] Forsham and Thorn In, Williams, Textbook of Endocrinology, 2nd Ed, Philadelphia, W B Saunders, Co p 224, 1955

g. ACTH tests

nt eosinophil fa

he excretion of

gmented freckles with a little increase in pigmentation of the skin creases the left elbow. The skin was coarse and the hair moderately fine. The ne age film showed normal bone development. The treatment consisted

one for

A total

Stanto

47th case is recorded by Brewlaw, Lashof and Klein.[103] Markovitz[104]

rtisone at first precipitated diabetic ketosis, but later more cautious use cortisone proved successful. The 50th case occurred in an adolescent scribed by Gould and Shlevin[106] with autopsy findings. Case 2 (12562),

ic 17-ketosteroids instead of increasing from a low level of 2 2 mg. per on Cortisone treatment fell to 1.4 mg and she had a severe hypo-cemic reaction She showed buccal pigmentation in 1949 when the

ulin The urine contained 4 0 per cent sugar and the blood sugar was 2 mg On January 24, 1952 her condition was improved Her treatment luded Cortisone 12½ mgms twice daily, insulin 30 units and the blood gar value was 219 mg She was doing well in April 1958

Our third case (1546), a physician practicing among tuberculosis patients, d at the age of sixty-nine years of Addison's disease, twenty-eight years er the onset of diabetes

The onset of diabetes mellitus in a patient with Addison's disease o had been intensively studied and had received adrenal cortical hor-ne therapy for four years was characterized by progressive anorexia,

glycemia occ
or exercise
clinical diabe
the institution of insulin treatment, and the food chosen changed from carbohydrate exclusively to include fatty foods A marked alteration in personality occurred with the development of diabetes The administration

ing increase in potassium excretion occurred. Later this patient's hypoglycemic states were checked by the use of Cortisone[108] In discussing 3 cases with 2 autopsies, Simpson[109] states that in 16 similar cases, 10 showed at autopsy atrophy of the adrenal, 3 had tuberculosis and 3 had hemochromatosis Other etiologic factors to be considered are metastasis from bronchogenic or other carcinomata, congenital hypoplasia, absence of basophil cells of the pituitary

Comparative effects of Compound E and other allied substances used in

proved exceptional

(*b*) **Cortical Hyperfunction.**—The ability of secretions of the adrenal cortex to initiate or augment diabetes mellitus in man is indicated in the patients with Cushing's syndrome and allied disorders Lukens[112] and co-workers reported that among 55 patients of proven tumor or hyperplasia of the cortex carbohydrate tolerance was impaired in 49 per cent and

according to Walters, Wilder and Kepler [113]

It is apparent that diabetes may occur in human beings as a result of extrapancreatic disease according to Ricketts[114] However, while hyperglycemia can be initiated by extracts of other endocrine organs such as the anterior pituitary, adrenal cortex and thyroid, it is still probable that the resulting damage to the pancreas is responsible for any permanent diabetic condition Furthermore, the clinical use of ACTH or Cortisone does not result in significant, permanent impairment of carbohydrate tolerance

CUSHING'S SYNDROME —While recognizing that certain cases were due to a primary adrenal disturbance, Harvey Cushing believed that in patients with a pituitary basophil adenoma and bilateral adrenal cortical hyperplasia the disease was primary in the anterior pituitary Albright sub-

[108] Thorn *et al*
[109] S
[110] S
[111] W
[112] L
[113] W , and Kepler Ann Surg
[114] Ricketts In, Progress in Clinical Endocrinology, edited by S Soskin, New York, Grune and Stratton, p 250, 1950

sequently demonstrated that the preponderance of corticoids over androgens was responsible for many of the signs and symptoms of the disease. The term "Cushing's Disease," formerly reserved for cases of bilateral adrenal cortical hyperplasia associated with a demonstrable basophilic adenoma, might now be applied to all cases of bilateral adrenal cortical hyperplasia, based on the concept that hyperplasia requires an excess of ACTH at one time or another. In contrast, the term CUSHING'S SYNDROME should be applied to the same clinical picture when the etiology is unknown or

In 51 cases

6 were male.

runk obesity

and striæ occurred in from 72 to 92 per cent of the series Diabetes was present in 26 per cent of the females and 33 per cent of the males The authors consider the Cushing's syndrome is undoubtedly an expression of increased elaboration and secretions of a group of adrenal steroids. The essential point is the discovery of accessible lesions, hypertrophy or tumor in the adrenals or elsewhere for surgical treatment. The most favorable lesion is the unilateral adenoma. Radiation of the pituitary has been strikingly successful in a few cases Temporary remissions occur.

Cases 13999 and 25930, the former consulting us for diabetes, the latter for obesity, had characteristic symptoms of diabetes, together with hypertension, high excretion of 17-ketosteroids, hirsutism, amenorrhea, loss of libido, purple striæ, lymphocytosis and osteoporosis. Both were treated with radiation. Case 13999 died August 24, 1949, four years later, of cerebral arteriosclerosis A small tumor of the pituitary was found at autopsy

Case 41891, aged 39 years had at the onset of diabetic symptoms in October 1952, blood pressure systolic 210 and diastolic 120, in March 1953, when the blood sugar value was 350 mg. a slight acne-form rash was present During the years from 1953 to 1956, the 24 hour urinary excretion of 17-Ketosteroids, determined at intervals, has tended to decline from initial levels of 30 4 and 34 7 to 18 0 mg in 1957 On October 10, 1958, her blood pressure was systolic 160 She is at work.

Case 25930, aged twenty-three years, had gained 27 pounds during the two years that followed her marriage. Spontaneous compression fractures of the thoracic vertebræ occurred with persistent severe pain. Headache and rapid progression of weakness occurred Exploration of the adrenals did not reveal any tumor. Trial with hormonal treatment was refused in favor of operation upon the pituitary gland Death followed within thirty-six hours. At autopsy a small basophilic tumor was found in the pituitary The diabetes in this patient was mild in contrast to the patient of Pullen and Sodeman[117] who presented many symptoms of Cushing's syndrome, obesity, changes in sex organs, hirsutism and hypertension. Their patient received 200 units of crystalline insulin daily without any pronounced

[115] Forsham and Thorn P 272, Loc cit, p 645
[116] Levine and Weisberg In, Progress in Clinical Endocrinology, Edited by S Soskin, New York, Grune and Stratton, p 100, 1955
[117] Pullen and Sodeman Jour Clin Endocrin, 3, 345, 1943

effect upon the carbohydrate metabolism and without insulin reactions Four cases of Cushing's syndrome with alkalosis, low blood potassium, no tumor, no hyperplasia of adrenal cortex and transient diabetes are reported by Claxton, Bennett, Power and Kepler.[118]

Case 29904, under treatment with ACTH for polyarteritis nodosa from July 1950 to February 1951, developed typical "moon facies" obesity and striæ. Death occurred in November, 1952

hing's syndrome in
y one (Case 32078),
All were women.

Diabetes preceded detection of hypertension, hirsutism, "moon" face, edema, and "buffalo" obesity by only 1 to 4 years. Proximity of the appearance date of diabetes to that of the other clinical features and its marked amelioration upon ensuing adrenalectomy indicate that increased glucocorticoids may have played an important role in etiology in all three cases One woman's insulin was reduced from 72 units to zero and in two others,

ig surgery However,

or therapeutic hyper-
corticism has evidently been reversible following removal of the steroid source, lasting diabetes has been claimed[119] as a result of prolonged ACTH treatment in a patient with rheumatoid arthritis

ADRENOGENITAL SYNDROME —Cortical hyperfunction with an overproduction of adrenal androgenic hormones has as its chief feature in postnatal development hirsutism and virilization in the female and sexual precocity in the male[120] Tumors or hyperplasia may result in cortical

may cause the dia-

had an adenoma of

(1) Cases with pseudohermaphroditism, (2) cases with virilism and (3) the Achard-Thiers syndrome in which the adrenal lesion is but one component of a multiple glandular disturbance Their own case, a thirty-year-old woman, only developed diabetes some years after the other symptoms of the syndrome Her father had diabetes, again emphasizing the importance of the diabetes heredity even when other glandular disorders are present in the diabetic Parts of each adrenal were removed surgically, but only after death was the adenoma found The diabetes was refractory to insulin chiefly because of the marked disturbance in metabolic processes resulting from the disease in the suprarenal cortex

One woman, Case 46829, with mild virilization, huge clitoris, and requiring only 8 units of insulin excretes 21 mg of 17-ketosteroids per day, but no treatment has been indicated to date, April, 1958

[118] Claxton, Bennett, Power and Kepler Ibid, 5, 61, 1945
[119] Bishop and Glyn Proc Roy Soc Med, 45, 168, 1952
[120] Shepardson and Shapiro Endocrinology, 24, 237, 1939

Aldosteronism.—Primary aldosteronism is now recognized as an entity and aldosterone-producing tumors can be clinically diagnosed. Aldosterone, one of the adrenal cortical steroids, is 20 to 30 times as effective as desoxycorticosterone in maintaining electrolyte balance in Addison's disease, and

one. His three cases, 2 female and 1 male, illustrated the typical findings of serum sodium values from 139 to 148 in mEq. and low serum potassium values from 1.7 to 3.0 mEq. per liter. In one woman, fasting blood sugar values were 309 and 406 mg. per 100 cc and the others showed abnormal *glucose tolerance tests. The diabetes associated with aldosteronism appears* mild. However, in one case it has persisted even after adrenalectomy.

2. Adrenal Medulla

... are composed of

contain as much as ... per cent of nor-epinephrine, which ... fourth the effect of epinephrine in causing a rise in blood sugar from a stimulation of glycogenolysis in the liver and muscles. Since 1941, five cases of pheochromocytoma and diabetes in which the latter was cured or markedly ameliorated by removal of the neoplasms have been reported. Four[126] of these patients had required insulin before operation and the fifth had a *definitely diabetic glucose tolerance curve.*

In Case 15370, removal of a large pheochromocytoma in 1938 had not been followed by a change in severity of diabetes up to death in 1948. In Case 23357, lobectomy for tuberculosis of lung was interrupted by sudden rise in blood pressure At autopsy, a pheochromocytoma in one adrenal was found

Although none of thes
dramatic amelioration of
two patients with onset
medullary tumor Dial
affected by operation, and he had developed retinopathy and albuminuria three years before hypertension was noted.

Comparison of five tests for pheochromocytoma was made by Evans *et al*[127] in 4 cases of surgically proven pheochromocytoma, 24 pseudo cases

[126] McCullagh Diabetes, *5*, 443, 1956, Howlett, McCullagh, Farrell, Dustan and Pe... Am. Med. Assn., ... 710, 1957.

1956 Duncan, Semens ... Med Assn, *151*, ... and Strickland ...

an ... 12 ... Canad Med Assn Jour, ...

[127] Evans, Rubitsky, Bartels and Bartels Am. Jour Med, ... 448, 1951

TABLE 123.—THREE PATIENTS WITH DIABETES AND PHEOCHROMOCYTOMA HAVE BEEN DIAGNOSED AND TREATED FROM FEBRUARY, 1954 TO SEPTEMBER, 1955

Patient	*Age at Diabetes Onset*	*Date Diabetes Onset*	*Date Removal Pheochromocytoma*	*Insulin Before Operation*	*Insulin After Operation*	*Heredity of Diabetes*
Case 10968 Female	40	1951	1954	30	0	+
Case 16129 Male	63	Jan., 1955	Sept 1955	24	0	0
Case 17180 Male	14	1934	1955	80	80	+

benzodioxane gave some false positives.

D. THE THYMUS AND DIABETES

In Major's[128] case, a child, aged eleven years, with diabetes of two years' duration, and occasional attacks of asthma becoming increasingly infre-

it

The necropsy showed edema of the lungs, an unusually large thymus covering the entire surface of the pericardium anteriorly and weighing about 50 grams The abdominal lymph glands were enlarged In the pancreas the islands were strikingly reduced in number but were without evidence of degeneration.

A case of adrenocortical hyperplasia, aged forty-six years, female is described by Wilder,[129] who had, in addition to frank adrenal virilism and *intense alkalosis associated* ... *5 cm. in* diameter. Sixty-five units ... of tetany occurred in her terminal ill... oke were present in the basophilic cells of the pituitary but no adenoma was found

Large doses of thymus hormone increased alimentary hyperglycemia, a result similar to that following anterior pituitary extract and failure of the anterior pituitary extract to produce results if the thymus is removed have suggested a possible role for thymus as a contributory factor in diabetes[130]

E PINEAL BODY

... with pineal ... ndary sexual

... activity has ... tay and Alt-schule[132]

F. DIABETES INSIPIDUS AND DIABETES MELLITUS

Diabetes insipidus may result from injury to the hypothalamus, posterior lobe of the pituitary or the bilateral pathways connecting the hypothalamus with the posterior lobe *All three links were involved in the patient which* Natelson[133] reported with co-existent diabetes insipidus, acromegaly and

[128] Major and Helwig Jour Am Med Assn, *86*, 1766, 1926
[129] Wilder Loc cit, p 71
[130] Bombskov and Klein Ztschr f klin Med, *139*, 96, 1941 Bombskov and Schweiger Ibid, *139*, 102, 1941
[131] Robson and Mendenhall Am Jour Clin Path, *26*, 283, 1956
[132] Kitay and Altschule The Pineal Gland, Cambridge, Harvard Univ Press, 1954
[133] Natelson: Ann Int Med, *40*, 788, 1954

diabetes mellitus in a 46 year old Mexican female who entered the hospital in diabetic acidosis Blood sugar was 720 mg and CO_2 of serum 11 vols per cent. Her photograph taken 3 years previously showed obvious acromegalic prognathism, coarsening of the features, macroglossia and

reported in 27 patients according to Lowrey,[124] of whom only 3 were children. Lowrey's case, a girl aged 7 years excreted 7000 to 10,000 cc. urine in 24 hours. The specific gravity never exceeded 1003. Three years later, she still required pitressin tannate 1 cc. daily and her insulin dose had increased from 23 to 33 units Bone growth had been normal Excretion

nancy in cases of diabetes insipidus.

Case 16762, male, had an extraordinary history of diabetes insipidus for six years with spontaneous relief. At the age of fifty-nine years he began to drink every five to fifteen minutes and passed urine at the same rate. He

duty in the Army. She required pitressin tannate by injection 2 to 3 times daily Diabetes mellitus was discovered in 1948 Following appendectomy in February 1952, her insulin requirement rapidly increased from 15 units until she took 600 units of globin and 400 units NPH insulin daily. On May 21, 1952 her first 24-hour urine amount was 2700 cc, glycosuria 1.7 per cent, blood sugar values 312 mg fasting, 333 mg at 11 A.M, and 494 mg at 4 P.M Insulin dose was 450 units in three divided doses. Pitressin tannate in oil was needed once in 2–3 days Death occurred one year later. Autopsy revealed marked bone marrow changes and the widespread invasion of tissues by non-lipid containing histiocytes, found in the bone marrow and in the posterior lobe of the pituitary, which resembled the cells in lipoid histiocytosis of the cholesterol type[127] (Hand-Schuller-Christian disease)

G GONADS AND DIABETES

At present men and women with adequately controlled diabetes have reproductive capacities comparable to healthy non-diabetic individuals A recent study[128] has confirmed this observation in a group of diabetic

[124] Lowrey Am Jour Dis Child, *80*, 69, 1950
[125] Greene and Gibson Jour Lab and Clin Med, *24*, 455, 1939
[126] Soule Am Jour Obst and Gynec, *33*, 878, 1937
[127] Rowntree and Poppiti Jour Am Med Assn, *150*, 310, 1951

men and controverts the finding of Jackson[139] that children of diabetic fat[illegible]

28 [illegible]

animals,[140,141] and in 5 of 6 acromegalic[142] patients, whose acromegaly and minimal diabetes were reversed.

Premature impotence is frequently seen in diabetic men, being especially common after many years of poorly controlled diabetes in patients with juvenile onset Diabetic neuropathy presumably is responsible (Chapter 18).

II. PARATHYROIDS

The association of hyperparathyroidism and extensive nephrocalcinosis has been reported in a series of 16 cases since 1940. Fifteen of the cases are referred to by Gross,[143] and the sixteenth case is described by Hoar and Gorlin [144] Six of the 15 patients were women The parathyroid lesion in 11 cases was adenoma, in 2 Wasserhelle hyperplasia, in 1 carcinoma and in 1 "tumor" In 8 of the 15 cases there were pancreatic calculi, and in 5 cases both pancreatitis and areas of pancreatic calcification were noted It has been suggested (1) that the hyperparathyroidism may have led to pancreatitis and (2) that pancreatitis and sequelæ may have led to hyperparathyroidism The hypercalcemia of hyperparathyroidism may favor calcific deposits within the pancreatic ductal system Gross points out, however, that information is lacking in regard to the calcium content of the external pancreatic secretion in cases of pancreatitis. Values for serum calcium were elevated in each of the 13 patients in whom such analyses were performed The practical point emerges that whenever areas of calcification in the pancreas are noted serum calcium values should be sought and the possible existence of hyperparathyroidism should be considered It is known that in experimental animals excessive parathormone can cause focal pancreatic necrosis Diabetes was present in certain cases, notably Case 3 of Gross' series, a 40 year old white man in whom chronic relapsing pancreatitis coexisted with hyperparathyroidism This man's father had diabetes The hereditary factor is stressed not only in recurring cases of pancreatitis, notably Case 2 in Gross' series, but is especially remarkable in the family reported by Jackson [145] In his report 6 and possibly 7 cases of hyperparathyroidism occurred in two generations of one family, associated with recurring pancreatitis in at least two instances. Without doubt two members of this extraordinary family had diabetes.

Chapter 27

DIABETIC CHILDREN AND THEIR LATER LIVES

PRISCILLA WHITE, M D

The Natural Course of Juvenile Diabetes.—In the natural course of juvenile diabetes the onset is typically acute Eight hundred seventy-three (21.5 per cent) of 4054 of our children reported the day or week of their onset of symptoms The early course is virulent in that the recognition of diabetes may be in chemical diabetic coma. Recognition in coma was true of all except one of our infants under age one, common up to age three, and in 15 per cent of all our juveniles.

In spite of this turbulent onset, a favorable phase follows. This partial remission is not dependent upon unique types of therapy, or even upon insulin It was observed both in the pre-insulin and the early insulin eras

patients is 30 per cent. Since many of our juveniles enroll in the Clinic years after onset and the details of early response are forgotten, this percentage under- rather than overestimates the frequency of the remission phase As omission of insulin is not permitted in our juveniles, the remission phase is designated when the daily dose falls to 2 or 4 units

Documentation of the remission phase by measurement of insulin-like activity was made recently in an adolescent, (Case 50845), aged 19, on the 30th day after recovery from diabetic coma, at which time she received 1600 units of insulin In comparison with the normal 100 to 185 microunits, this patient showed more than 300 microunits of insulin-like activity in the blood

The duration of the remission phase varies from three months to nearly three years but is usually lost within the first year The factors terminating it are for the most part not preventable and include linear growth, puberty, respiratory infections and acute infectious diseases.

Gradual intensification of the diabetes follows the remission Between the third and fifth years, total diabetes develops. The evidence in favor of this concept is clinical, chemical and structural Clinical evidence is found in the disproportionately increased requirement for long-acting insulins to control nocturnal hyperglycemia and the response to sulfonylurea drugs, which is in inverse ratio to duration of diabetes The response to a test dose among 300 of our children so tested was 90 per cent when duration of diabetes was under 6 months, 60 per cent at the end of the first year, 40 per cent in two years, 30 per cent in three, 10 per cent in five, and 6 per cent thereafter

42

The quantity of extractable insulin in the pancreas of long-term juvenile diabetics has been found by Wrenshall[1] to be 0 to 10 per cent, and no assayable insulin-like activity was found in the blood of long-term juveniles by Bornstein.[2]

Diminution in size, number and differentiation of islets was found in 93 per cent of 31 autopsied cases Low mean weight of beta-cells has been reported by Maclean and Ogilvie.[3] Disappearance of granules has been reported by Bell[4] All this implies that the total or near-total diabetic state is eventually acquired by the juvenile diabetic.

In spite of this profound degree of the metabolic disturbance, linear *growth proceeds satisfactorily. The median height finally attained by the* males in 1072 twenty-year juvenile survivors was 68 inches and by the females was 63 inches. The age of menarche of diabetic girls with onset under eleven was delayed to 13 96 years, and although fertility rate was [illegible]

[illegible] twenty years' exposure, 1072 juvenile cases had had coma in 52 per cent of females and 39 per cent of males, sepsis in 33 per cent of females and 30 per cent of males, neuropathies in 26 per cent of females and 20 per cent of males, and eventually vascular damage was recognized in 94 per cent Since the potentially lethal characters of coma and sepsis have been corrected, the prevention and control of vascular damage remain the problem

A. INCIDENCE

Juvenile diabetics, defined as those patients with onset under fifteen *years of age, comprise 5 per cent of all diabetics Because of many special* programs designed for their care, they comprise 10 per cent of Joslin Clinic patients In the United States today some 150,000 individuals are surviving the childhood form of the disease Among children, 1 in 2500 under age 15 is a diabetic

In childhood diabetes the sex distribution is nearly even; 1970 (48 6 per cent) of our 4054 cases were males and *2084 (51 4 per cent) were females* The most common age of onset is 11 years The actual sex and age distribution of the cases is shown in Figure 30 Girls, coincidental with their earlier puberty, had a slightly earlier peak of age at onset, 10. The peak age for boys was 13 The ages with lowest frequency are those where the ratio of islet to pancreatic growth is high and the highest diabetes incidence is found in those ages where islet growth in proportion to total pancreatic growth is slow

The ratio of Jewish children to total is 7 per cent

B ETIOLOGY

*Because of the many opportunities to recheck family histories, the heredi-*tary predisposition to diabetes was revealed in 57 per cent of 1072 child-

[illegible] ...tes, *1*, 87, 1952

[illegible] our , *1*, 732, 1951

hood cases surviving 20 years of diabetes In 13 per cent parents were diabetic, in 18 per cent grandparents, and in 1 per cent, offspring were diabetic The incidence of positive heredity in the entire series of 4054 patients at first visit, which was not necessarily close to onset, was 41 6 per cent.

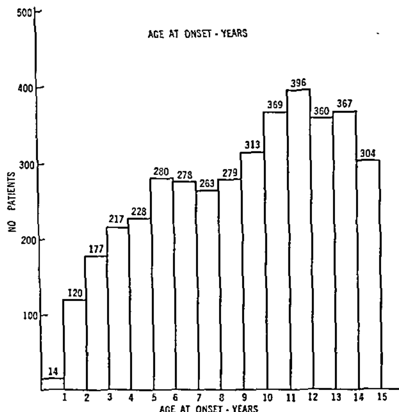


FIG 29 --Age at onset, years—juvenile diabetics

The evidence in favor of the hereditary transmission of diabetes is as follows. (1) the incidence of diabetes in similar twin mates, which is 50 per cent, (2) statistically significant excess of diabetes in the close blood relatives of diabetics (in their parents and siblings this amounted to 7 times the incidence in the control population), (3) the demonstration of Mendelian ratios of the recessive type in cases reporting in sequence, (4) the demonstration of Mendelian ratios of the recessive type in families tested with glucose tolerance tests

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In spite of this profound degree of the metabolic disturbance, linear growth proceeds satisfactorily. The median height finally attained by the males in 1072 twenty-year juvenile survivors was 68 inches and by the females was 63 inches. The age of menarche of diabetic girls with onset under eleven was delayed to 13.96 years, and although fertility rate was high, the eventual fetal wastage was 40 per cent.

During their diabetic lives these patients are exposed to three potentially lethal complications, ketoacidosis, sepsis and vascular disease After twenty years' exposure, 1072 juvenile cases had had coma in 52 per cent of females and 39 per cent of males, sepsis in 33 per cent of females and 30 per cent of males, neuropathies in 26 per cent of females and 20 per cent of males, and eventually vascular damage was recognized in 94 per cent Since the potentially lethal characters of coma and sepsis have been corrected, the prevention and control of vascular damage remain the problem

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In childhood diabetes the sex distribution is nearly even; 1970 (48.6 per cent) of our 4054 cases were males and 2084 (51.4 per cent) were females. The most common age of onset is 11 years. The actual sex and age distribution of the cases is shown in Figure 30. Girls, coincidental with their earlier [illegible]
peak age for [illegible]
the ratio of [illegible]
incidence is found in those ages where islet growth in proportion to total pancreatic growth is slow

The ratio of Jewish children to total is 7 per cent.

B ETIOLOGY

Because of the many opportunities to recheck family histories, the hereditary predisposition to diabetes was revealed in 57 per cent of 1072 child-

[illegible] tes, *1*, 87, 1952
[illegible] ur, *1*, 732, 1951

year of onset, 90 per cent had none. The experience of Grishaw, West and Smith[5] is similar. They report an incidence of infection in 20 per cent of their cases in the year of onset. John,[6] Lande,[7] and Brown,[8] however, found a relatively higher incidence of infections prior to the onset of the disease, while Danowski[9] reports 42 per cent The relative frequency of infections in the year of onset in the 504 children studied carefully in this respect is shown in Table 124 The peak for incidence in January among our cases, however, suggests the influence of infections

TABLE 124 —INFECTIONS IN THE YEAR OF ONSET OF 504 DIABETIC CHILDREN

Pertussis	12	Tonsillitis	5	Adenitis	2
Measles	10	Mumps	3	Appendicitis	1
Chickenpox	8	Influenza	3	Diphtheria	1
Scarlet fever	7	Jaundice	2	Rheumatic fever	1
Coryza	7				

TABLE 125 —MONTH OF ONSET OF 3831 DIABETIC CHILDREN

January	537	July	403
February	279	August	283
March	292	September	378
April	260	October	247
May	252	November	288
June	332	December	333

Trauma, Psychosomatic Disturbance, Obesity.—Trauma, important

of the children at onset of diabetes had exceeded their expected weight for age Since growth peculiarities, especially large size, have been found to characterize the offspring of diabetic mothers, the birth weights of juvenile diabetics have been recorded and show no significant deviation from normal

C PREDIABETES

A prediabetic state appears to be recognizable in the juvenile population This includes the adolescent spurt of growth and sexual maturity, the occurrence of congenital anomalies, changes in the bulbar conjunctiva, hypoglycemia, high titres for FSH, and possibly increased excretion of 17-ketosteroid

Med , 64, 787, 1939

mphasis on Children and Young Adults,

Secondary factors permitting the expression of the gene are presupposed because the clinical signs and symptoms of diabetes are not evident at birth or soon thereafter.

Infections.—Acute infections have not appeared to play a frequent role in the etiology of our diabetic children. Whereas 10 per cent of 504 cases in a pilot study reviewed with great care had an infection of severity in the

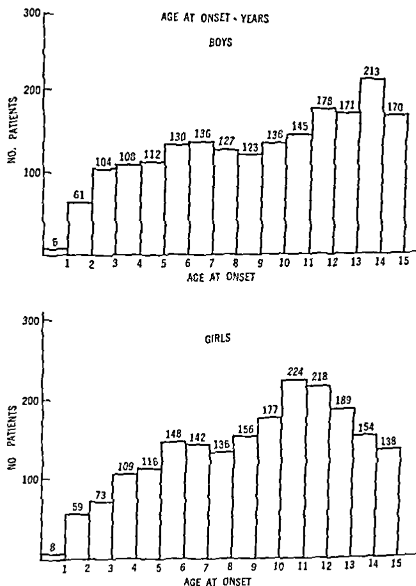


Fig 30 - Age at onset, years—boys and girls

and Meredith in Figure 31. The heights exceed the expected for age by one year.

	Number	*Age, Years*
Cincinnati, born in 1919	246	13 09
Southern England	2590	13 49
North Carolina, born in 1918	669	13 31
Kansas, born in 1919	295	13 15
Wisconsin, born in 1921	775	13 22
Diabetics	204	12 84

FIG 33 — Menarche in Six Groups of Girls

At the time of diabetes onset, the average bone development of diabetic children, compared with that shown for normals in the Todd Atlas, was found by Bogan and Morrison[10] to be 18 months in advance of the chronological age, and the dental development was found by Robinson[11] to be 12 months in advance.

In a study by Wagner, White and Bogan[12] the development of hips and breasts, appearance of pubic and axillary hair and menarche occurred earlier in the short-term diabetics than in normal controls or in long-term diabetics, and recently Post and White[13] found in 204 girls whose dia- [illegible] ie which appears

[illegible] and Bogan[14] to [illegible] These anomalies were usually minor, as follows: Dupuytren contractures, curved fifth finger, brachydachtylia, brachycephalus, ear nodule on the lateral aspect of the auricle.

The vascular pattern of the bulbar conjunctiva in a group of offspring of diabetic mothers was found by Ditzel *et al* to resemble that of diabetics These changes were not found in normal controls.

prepared serum in contrast to 13 per cent positive reactions in 22 comparably aged non-diabetic controls. The 17-ketosteroid excretion of 40 newly contracted cases of diabetes and 15 children of diabetic parents showed higher excretion levels than did the non-diabetic controls

These changes have been interpreted variously as the results of hyperpituitarism induced by the gene They have also been attributed to a pleiotrophic effect of the diabetes-producing genotype (apparently unrelated to the overt disease)

White Dia-

387 measured within 3 months of onset
D.M
N.
HEIGHT INCHES
70
60
50
40
30
20
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
AGE AT ONSET

Fig 31 —Heights of 387 girls measured within 3 months of onset of diabetes

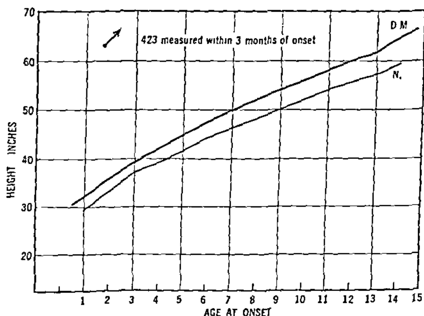


Fig 32 —Heights of 423 boys measured within 3 months of onset of diabetes

[illegible]

one year.

	Number	Age, Years
Cincinnati, born in 1919	246	13 09
Southern England	2590	13 49
North Carolina, born in 1918	669	13 31
Kansas, born in 1919	295	13 15
Wisconsin, born in 1921	775	13 22
Diabetics	204	12 84

Fig 33 —Menarche in Six Groups of Girls

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Congenital anomalies were reported by Wagner, White and Bogan[14] to occur more often in the diabetic than in the control children These anomalies were usually minor, as follows. Dupuytren contractures, curved fifth finger, brachydachtylia, brachycephalus, ear nodule on the lateral aspect of the auricle

The vascular pattern of the bulbar conjunctiva in a group of offspring of diabetic mothers was found by Ditzel *et al* to resemble that of diabetics These changes were not found in normal controls

[illegible]

prepared serum in contrast to 13 per cent positive reactions in 22 comparably aged non-diabetic controls The 17-ketosteroid excretion of 40 newly contracted cases of diabetes and 15 children of diabetic parents showed higher excretion levels than did the non-diabetic controls

These changes have been interpreted variously as the results of hyperpituitarism induced by the gene They have also been attributed to a pleiotrophic effect of the diabetes-producing genotype (apparently unrelated to the overt disease)

[10] Bogan and Morrison Am Jour Med Sci, *174*, 313, 1927
[11] Robinson [illegible]

White Dia-

D. SYMPTOMS AND SIGNS

The characteristic symptoms of diabetes are almost invariably present in the child. Those most frequently reported are polyuria, polydipsia, polyphagia, loss of weight, loss of appetite, pruritus, furunculosis, alternat-

E. DIAGNOSIS

Errors in the diagnosis of diabetes in childhood arise from the fact that glycosuria is common in children. Thus children may be treated with dietary restriction and insulin before an accurate diagnosis is established, as with adults. The diagnostic levels for "true" glucose Somogyi-Nelson

time 20 mg. may be accepted as normal.

Glucose tolerance tests are used if the diagnosis of diabetes is not established by *random blood and urine analysis. The preparation of the child* for a glucose tolerance test is as important as preparation of the patient for a basal metabolism test or for *x*-ray examinations. Fever, prolonged bed

rest during the test.

In the oral test, the dose of glucose used under age three is 3 grams per other age groups the normal test dose body weight. Such amounts of glucose who weigh less than 100 pounds. To children weighing over 100 pounds, the adult quantity, 100 grams of glucose is given. Obese children who have abnormal curves when they *have received glucose according to actual body weight are retested with* the quantity of glucose which is based upon their ideal weight for height and age. For practical purposes we use 1 gram of glucose per pound of body weight. Danowski[18] recommends 2.5 grams under 18 months and 2 grams *18 months* to 2 years.

The blood sugar is obtained fasting, after one-half, one and two hours for venous curves, and preferably an additional hour for capillary curves. The diagnosis, as with the adult patient, is based upon the peak rather than upon *the fall of the curve. If the Exton-Rose test is employed,* the quantity of glucose is again calculated on the basis of body weight. The total quantity is divided into equal parts, one administered fasting, the other one-half hour later.

18 Danowski. Loc. cit., p. 659.

Danowski[16] has found that the lowering of inorganic phosphorus from plasma following carbohydrate loading failed to differentiate juvenile diabetic from non-diabetic children. In untreated diabetics the potassium levels rose abnormally after glucose. Serum bicarbonate showed no change or fall in contrast to the rise in controls. Chloride and sodium fluctuated at random in both groups In general, these indices proved disappointing in separating diabetics from non-diabetics

Unclassified glycosuria, renal glycosuria, and potential diabetes (5 per cent of our juvenile population) designate the same types of glycosurias as they do in the adult population Of some importance in the juvenile population are the melliturias with excretion of sugars other than glucose, namely, pentose, levulose, lactose and galactose Renal glycosuria has been demonstrated in 12 Joslin Clinic diabetic children, essential levulosuria in 2 and essential pentosuria in 7 Lactosuria has not been sought It is a physiological finding in the nursling Galactosuria may be found in children with digestive disturbances

F HISTO-PATHOLOGY

Pancreas.—Significant variations in the relative rate of growth of islet tissue have been observed Under two years of age the rate of islet growth parallels that of the pancreas as a whole Between the ages of 4 and 12 years the relative rate of islet growth falls to about one-half of the rate of the entire pancreas In adolescence the rates of growth become equal again After the age of three the number of islets remains

As in the adult, Warren and LeCompte have emphasized that the chief characteristic is the wide variety of lesions observed in a single pancreas, suggesting an agent destroying islets and permitting regeneration

General Pathological Changes.—In juvenile diabetes these have varied with four therapeutic periods as follows preinsulin, early, mid- and late insulin eras The preinsulin changes were the chemical rather than the histological ones of diabetic coma Cerebrocapillary dilatation, peri-vascular edema, degeneration of the central nervous system and toxic tubular nephritis were observed Fatty infiltration of the liver was a constant finding and lipoid histiocytosis of the reticuloendothelial system was reported

In the early insulin era, 1922 to 1930, juvenile diabetics examined by Warren had survived on the average about two years of diabetes The abnormal distribution of glycogen and fat was the most striking change observed by the pathologist Fatty infiltration of Kupffer's cells of the

[16] Danowski Loc cit p 659
[17] Warren and LeCompte Chap 11, Loc cit, p 170

liver, of the spleen pulp, of the intima of the aorta and of the skin was shown [illegible]

in the skin, muscle and cytoplasm of the liver cells. Atherosclerosis was found in 30 per cent. With the more skillful use of insulin the above changes became less conspicuous, and the postmortem examinations in the mid-insulin era, 1930 to 1940, showed the ravages of sepsis including pyelonephritis, metastatic abscesses of the liver, heart, lung, spleen and brain In the diabetic child, as in the general population, chemotherapy and antibiotics have altered the course of fatal sepsis In this era the fatal cases which were studied had survived five years of diabetes. All showed evidence of atherosclerosis.

In the late insulin era, 1940 to 1957, the duration of diabetes in fatal cases coming to autopsy at the New England Deaconess Hospital exceeded fifteen years. Nearly all were in the third or fourth decade of life and all with over 15 years' duration showed intercapillary glomerulosclerosis with or without pyelonephritis. Although the emphasis in youth is on the damage to renal vessels, widespread involvement of coronary, cerebral and other vessels occurs with advancing age and duration.

G. MANAGEMENT OF JUVENILE DIABETES

Our fundamental principle of management of juvenile diabetes is the regulation of insulin and diet to enhance both physiological and chemical control

Insulin.—CHOICE OF INSULINS —The choice rests among quick-acting [illegible]

glycemic action Regular and semi-Lente insulins act quickly By the subcutaneous route they commence the hypoglycemic action within an hour of administration, reaching peaks in three to four hours and lasting six to eight hours Of the intermediate-acting insulins, Globin starts its *action within an hour, NPH and Lente start within two hours*, all reach a maximum effect eight to ten hours after administration and last approximately twenty-four hours (Globin the shortest, NPH between, and Lente [illegible]

and 1 of regular and 1 of protamine

The two long-acting insulins, protamine zinc and ultra-Lente, have little hypoglycemic effect for 6 to 8 hours, maximum effect 12 to 24 hours, nearer 24, and last 36 hours, with weak action up to 72 hours One more property of protamine zinc insulin should be emphasized, the ability to adsorb regular insulin This is due to the excess of protamine which has been added and is why in mixtures the effect is reversed

The effect of the size of the dose of insulin upon the *time-action curve*

is of great therapeutic importance Increase in the dose of regular insulin primarily increases the depth to which the blood sugar falls. Increase in the dose of protamine zinc increases duration of action, and increases in doses of intermediate insulins increase intensity and duration of action The principle is not perfect. Massive doses of regular insulin given to

and is more effective in patients having a low kidney threshold Some pediatricians prefer to treat infants the first year or two with quick-acting insulins, although for the juvenile diabetic their prolonged use is unwise It would be successful if given by the clock, but in the hands of patients the frequency of the injection may be twice in 24 hours or even once, so

Among the intermediate-acting insulins, the first choice for allergic children is Lente. In the juvenile population Globin and Lente have one common objection They are slightly more painful than NPH The 2:1 mixture of protamine and regular has had wide use The 3 1 mixture is limited almost exclusively to the young population, under age 5, where the requirement for rapidly-acting insulin is high and for the long-acting insulin low. A specific indication for protamine zinc insulin today is for the occasional patient in whom the control of nocturnal hyperglycemia is most difficult Usually a split schedule of intermediate-acting insulin is desirable,

e alone or in combination with

patients with allergies, who may have to be desensitized U-500 regular insulin is used exclusively in the

one-quarter of a unit per pound, or at one year, 5 units, at 5 years, 10 units, at 10 years, 20 units, and at 15 years, 30 units

REGULATION OF INSULIN – There are two concepts concerning the regulation of the dose of insulin, one to correct glycosuria and the other to anticipate it With intermediate and long-acting insulins, anticipation appears more logical The depot of insulin with its constant blood sugar lowering action should be remembered In regulation, tests at three times during the day are the most valuable. The second of two voided specimens pinpoints the metabolic behavior and is closer to the blood sugar level

A poor test before the evening meal indicates that the patient has not received enough intermediate-acting insulin. If the specimen before the evening meal has become sugar free but the pre-breakfast specimen contains significant quantities of glucose, a dose of intermediate-acting insulin may be added at bedtime The pre-breakfast test becomes the guide for regulating the bedtime dose of insulin. Control is satisfactory if the patient is excreting less than 5 per cent of his carbohydrate intake, and for the majority of dietary prescriptions today this will place the loss at between 5 and 10 grams.

Variations in this prescription may be necessary. Sometimes regular insulin should be mixed with the bedtime dose of intermediate. Often one has to prescribe these mixtures earlier before the evening meal in order to [illegible] to bedtime.

[illegible] age of insulin are best made [illegible] should be only a unit at a [illegible]

desensitizing the patient with many small doses It is obvious that these patients should never again omit insulin

Insulin presbyopia is transitory but it is often wise to warn patients of its possible occurrence It is not impossible for patients to enter the hospital with 20/20 vision and leave unable to read. One should not permit refraction, unless absolutely necessary, for four weeks

Insulin edema we see in patients mildly acidotic and extremely undernourished

Oral Substitutes — In addition to the management of juvenile dia- [illegible] s, sulfonylureas [illegible] tion of sulfony- [illegible]

presence of endogenous insulin is necessary for effect In 300 children tested, the effect was in inverse ratio to duration of diabetes, as previously described, so that its use in the practical therapy of juvenile diabetes is not recommended

In addition to its hypoglycemic action, an antidiabetic effect was explored, since it was shown in animal experiments to produce islet hypertrophy and hyperplasia In our experience it did not prolong the remission

phase, did not appear to potentiate the action of insulin, and did not replace insulin therapy in part. Its use in youth is limited to questionable prediabetics

In the past eighteen months, some 100 juveniles have received DBI for various reasons These included cases with severe retinopathy demonstrating a favorable effect, diminution of venular dilatation in the bulbar conjunctiva, newly contracted juvenile diabetes, the more insulin sensitive, the most difficult to control In new cases it has proved effective without exogenous insulin for the period of trial, namely, twelve months, and during this period linear growth and gain in weight followed the expected normal course It replaces 50 per cent of the insulin easily bringing about better control in long-term, insulin-sensitive cases and diminishes frequency and severity of hypoglycemic reactions

The use is difficult; the time action curve resembles regular insulin, maximum effect in four hours, duration eight hours, so that the requirement is two, three or four times in 24 hours.[17a]

The current side effects of nausea, dry mouth and brassy taste, when more than 200 mg are prescribed, limit its present use.

Islet Protector Substances.—An attempt to prolong the remission phase was made in short-term patients Following the report of Houssay *et al*[18] that estrogen, cortisone, hydro-cortisone, and thyroxin, administered to rats made diabetic in several ways, induced correction of the chemical signs of diabetes and produced islet hyperplasia and hypertrophy, cortisone and thyroxin were given a three-year trial. Our clinical experience with former juveniles receiving estrogen and progesterone during pregnancy was suggestive of a possible favorable outcome Fifty per cent showed a 50 per [illegible]

cent

50 [illegible]

of the cases The 25 children treated with thyroxin followed the natural course of diabetes previously described

The adolescents treated with cortisone 5 to 15 mg daily, which was subdiabetogenic for them, had a more than expected favorable course One striking patient, Case 44053, now in his fifth year of diabetes, receives no ins[illegible]

be

their own infants dying neonatally One whole pancreas, three fragmented pancreases, and one in a millipore chamber were implanted in the thigh or abdominal rectus muscles While no untoward effects were observed, the insulin requirement did not differ from that observed following other pregnancies and the [illegible]

the

to

Overinsulinization, recommended by Brush,[19] to produce the remission phase, was widely accepted by pediatricians after his initial report Time

[17a] Krall *et al* Loc cit p 310
[18] Houssay, Rodriquez and Cardeza Endocrinology, *54*, 550, 1954
[19] Brush Loc cit, p 61

proved that the remission phase was not prolonged following his management and occurred in the natural course of diabetes.

Dietary Treatment.—The caloric prescription must be adequate to *maintain rates of growth normal for the individual child.* Calories may be prescribed by one of several rules—by age alone: at year one, 1000 calories added for each growth year; by weight and age: 100 calories/kg at age 1; 80 calories/kg. at age 5; 60 calories/kg. at age 10, 40 calories/kg. at age 15; by height: 35 calories per inch; by theoretical basal metabolism plus 80 per cent. These diets should be increased by 20 per cent for unusual activity. Such rules are modified for individual needs.

Because of obesity among adolescent girls, at age 13 their dietary prescription may be reduced to 30 calories/kg. of ideal body weight for height

is useful in practical therapy. The normal partition, derived from the formula of milk, is carbohydrate 50 per cent, protein 15 per cent, fat 35 per cent of the total calories. In the diets of the juvenile patients of the Joslin Clinic the carbohydrate does not exceed 40 per cent of the total calories, the fat is usually 40 per cent and the protein 20 per cent. The range of carbohydrate has varied from 100 to 200 grams. Diets high in carbohydrate are avoided, because they favor the development of wide fluctuations of blood glucose levels and extreme degrees of postprandial hyperglycemia

For rapid calculation, the carbohydrate in grams is 10 per cent of the figure for the total calories, and the protein and fat are approximately half the figure of the carbohydrate Thus, according to our rule for age, the child of nine requires 1800 calories, 10 per cent of that figure gives carbohydrate 180, halved for protein and fat gives 90 (or 1890 calories). The maximum carbohydrate prescribed is 225 grams After age 13 the protein and fat portions of the diet are increased for diabetic boys

Not only the quantity but the quality of diets remains important, the carbohydrate low in concentration, the protein of high biological quality,

Freston and Loughlin[20] reported the vitamin deficiencies at Camp Nyda *to be 27 per cent in 93 children The report of Mosenthal and Loughlin*[21] showed vitamin A deficiency in 68 per cent, B in 25 per cent and C in *4 per cent Hypercarotinemia was present in 28 per cent* At the Clara Barton Birthplace Camp, 130 children were tested for vitamin C in 1938, and no subnormal values were found During years of depression we found clinical signs of vitamin A deficiency, during war restriction, vitamin B deficiencies were found to predominate Dark adaptation was normal in *a small group of our children tested, none has given a history of night*

[20] Freston and Loughlin New York State Jour Med, *42*, 1833, 1942
[21] Mosenthal and Loughlin Arch Int Med, *73*, 391, 1944

TABLE 126.—SAMPLE DIETS

Egg	Meat	Bacon	Vegetables 3%	Vegetables 6%	Oatmeal	Butter	Cream	Milk	Orange	Potato	Bread
Carbohydrate 121, Protein 52, Fat 59, 1223 Cal											
1					15	5		240	100		
	30		75	38		7.5		240	100		15
	30		75	38		7.5		240	100		15
May split cereal portion into 60 cereal + 10 gm bread			Forenoon	1 Uneeda		Afternoon	2 Uneedas or 100 Orange		Bedtime	2 Uneedas or 100 Orange	
Carbohydrate 140, Protein 61, Fat 71, 1443 Cal											
1					15	5		240	100		15
	30		75	38		10		180	100		15
	30		75	38		10		180	100		15
Forenoon	1 Uneeda			Afternoon	2 Uneedas + 180 milk			Bedtime	2 Uneedas + 180 milk		
Carbohydrate 163, Protein 72, Fat 97, 1633 Cal											
1					15	5		240	100		15
	45		75	38	1	10		180	100		30
	45		75	38		10		180	100		30
Forenoon	2 Uneedas			Afternoon	2 Uneedas + 180 milk			Bedtime	2 Uneedas + 180 milk		
Carbohydrate 183, Protein 83, Fat 88, 1856 Cal											
1		15			15	5		240	100		30
	60		150	75		10		240	150		30
	60		150	75		10		180	150		30
School Recess	100 orange			Afternoon	2 Uneedas + 120 milk			Bedtime	2 Uneedas + 180 milk		
Carbohydrate 202, Protein 92, Fat 98, 2058 Cal											
1		15			15	10		240	100		30
	60		150	75		10		240	200		30
	90		150	75		10		210	150	75	30
School Recess	2 Uneedas			Afternoon	2 Uneedas + 120 milk			Bedtime	2 Uneedas + butter or peanut butter		

The carbohydrate for the day may be divided into even thirds, or one-fifth at breakfast, two-fifths at noon and at night. *Thirty grams of carbohydrate are subtracted to be given as two or three small lunches between meals and bedtime.*

blindness, but characteristic skin lesions occur. Faulty utilization of vitamin A is formed in the liver by the splitting of carotene, a lack may be inferred.

The calcium content of our diets exceeds 1 gram. If adequacy can be measured by incidence of osteoporosis our diets are adequate. Bone atrophy has been exceptional since 1926. Serum determinations for calcium and phosphorus show the former to be normal, the latter usually slightly below normal.

Emergency Diets.—The diet during acute infections may be reduced to carbohydrate 150, protein 50, fat 50 grams, consisting of eggnogs, milk and fruit juices. A simple rule is an alternate glass of fruit juice or eggnog every two hours for seven feedings The surgical patient should receive 75 to 100 grams of glucose parenterally, preferably as a 5 per cent solution.

For other plans of treatment, see Barach,[22] Boyd,[23] Escudero,[24] Wilder,[25] Stolte,[26] Lichtenstein,[27] Colwell *et al.*,[28] Jackson and McIntosh,[29] and Danowski.[30]

Exercise.—The third part of the treatment is of great importance, namely, exercise, the timing of which should be somewhat different from that of the child without diabetes, post-meal being favored over pre-meal exercise periods The

diabetes is that it actu

extracts have been fou

has been found to incre ... gars.

atients

ma ... visits

are

Readjustments of treatment are made on the majority of our children at summer camp units where the activity is normal Group psychology is helpful in solving the problems of the children.

II PSYCHOLOGICAL PROBLEMS

Because of the unusual medical responsibility which the details of treatment, menu planning, chemical testing, administration of therapy hypodermically, because of the stress produced by the sudden development of critical

edge

s, over-indulgent,

The over-anxious parent may precipitate anxiety states in the child, dependence or defiance, the overly-indulgent,

[22] Barach Am Jour Digest Dis, *11*, 350, 1944
[23] Jackson, Boyd and Smith Am Jour Dis Child, *59*, 332, 1940
[24] Escudero Inst Nac Nutricion, Buenos Aires, Recop Trab Acnt, *5*, 200, 1940
[25] Wilder Loc cit, p 71
[26] Stolte Med Klin, *28*, 831, 1931
[27] Lichtenstein Nord med Wchnschr, *10*, 1329, 1935
[28] Colwell, Isso and Stryker Arch Int Med, *69*, 931, 1942
[29] Jackson and McIntosh Proc Cent Soc Clin Res, *17*, 74, 1944
[30] Danowski Loc cit, p 659

exploitation; the perfectionist, deception and rebellion; the fourth, the *indifferent, depression, more rarely rebellion*

Self-management when the child is ready, should be encouraged, as well as diabetic undercentralization. The exploration for and the development of aptitudes is important Regular emotional support will help in the solution of his problems. Reassurance for a normal social, recreational, economic future life should be given repeatedly The anticipation of pleasing projects at frequent intervals, such as every three months, is a *must* for the child with chronic disease *Expertness in dietetics is a specific* need for the solution of the adolescent's social life, as is a substitute for food hunger in the form of extra affection for the very young diabetic. Summer camp programs dispel the feeling of being different and, finally, the value of the group therapy should be explored

Summer Camps.—The first camp for diabetic children was started by the late Dr Wendt in Detroit. Our own camp program had its simple beginning when a Deaconess nurse took one child to her home in Maine for the summer The result was excellent and in the subsequent year, 1927, she was persuaded to take five children and gradually expanded her work, until the time when her own health failed In 1932, our first group of children was sent to the Clara Barton Camp in North Oxford Ninety children can be cared for at one time for 3, 6 or 9-week periods. This camp is supported equally by The Association of Universalist Women, The Dia- [illegible]

FORECAST

Summer camps for diabetic children supplement hospital and office management Group psychology is beneficial Patients may be taught [illegible]

the resident physician, three nurses, three laboratory technicians and a dietitian for each camp The physical activity is that of a regular camp However, diets are weighed Daily quantitative and qualitative urine tests are done Serial blood sugars are estimated once or twice weekly

I BEHAVIOR PROBLEMS

Close adherence to the prescribed routine is the rule in the first year of treatment The child may have pride in hypodermic injections, testing outfits, etc After the first year, the routine of treatment palls. Indiscretions occur Up to the time of adolescence the child may be coaxed back

Joslin New England Jour Med, 235, 442 476, 1946

A D A Forecast, 11, 4, 1958

to routine, but in adolescence medical rejection parallels parental rejection. The diabetic routine does not favor the social success of the patient. Unity of behavior pattern and fastidiousness conflict with the prescribed diabetic treatment. Complete break in the control of diabetes occurs only *too often. With the normal diabetic child the rejection rarely lasts more* than two years. If the rejection is long and bizarre, psychiatric study is indicated. Abnormal electroencephalograms suggesting psychomotor behavior should be investigated Self-induced hypoglycemia or coma, pseudo cures and repeated hospitalization require psychiatric evaluation. Incor*rectly kept (perfect) urine charts, the substitution of water for a specimen of urine, the substitution of an obliging* normal friend's urine for the patient's own, while annoying to the physician, should not be considered abnormal behavior for the juvenile diabetic. Such acts do not require a psychiatric consultation

J. INTELLIGENCE OF THE DIABETIC CHILD

[illegible]

K PHYSICAL EXAMINATION

The physical examination of the diabetic child after several years' duration, compared [illegible]
wider range of heigh [illegible]
frequently in the c [illegible]
White and Bogan [35] [illegible]
of height and weight for a diabetic group

The skin, except for xanthosis, shows no common difference The teeth show less evidence of caries, hardly more than physiological caries of the sixth and twelfth molar was observed Pyorrhea, usually of only slight degree, occurred more frequently in the diabetics than in the nondiabetics Systolic heart murmurs are heard more often These are functional, not organic The liver is palpable more often, and there is more evidence of congenital anomalies of the mesenchymatous tissue, such as ear nodules, clubbed fingers, curved fingers and webbed toes.

Of the secondary sex characteristics, the early ones are often precipitated and the late ones postponed The me [illegible]
hormone and of 17-ketosteroid show [illegible]
reference to the latter, the excretion o [illegible]
and later falls to subnormal values Free corticoids in serum were found by Klein *et al* [37] to be related directly to glycosuria and inversely to CO_2 content

[34] Brown and Thompson Am Jour Dis Child, *69*, 238, 1940
[illegible] England Jour Med, *223*, 119, 1940
[illegible] Child, *64*, 1833, 1942
[illegible] atrics, *17*, 214, 1956

The follicle-stimulating hormone is elevated at onset, falls to low values and then may rise again.

L STANDARDS FOR CONTROL

Perhaps the most debated question in the management of the juvenile diabetic today concerns itself with the degree of chemical control. Three schools of thought regarding control of diabetes exist: (1) that which advocates perfect chemical control; (2) that which advocates good but not quite perfect chemical control, (3) that which advocates clinical but not chemical control of the disease The proponents of perfect and good con- control of diabetes maintain that the degenerative complications are precipitated by chemically uncontrolled diabetes, whereas those who favor clinical over chemical control of diabetes believe that the degenerative complications of diabetes are caused by diabetes *per se* rather than by its [illegible]

M DIABETES IN INFANCY

A most complete report of diabetes in infancy (onset under twelve [illegible] ell [illegible] nty [illegible] 16

are alive with durations of diabetes ranging from less than one to twenty-five years Case 5459, at the age of thirteen, had the physical development of eighteen years and the highest I Q ever observed by an examiner with much experience in private schools

Complications such as acidosis, skin lesions, and gangrene have been reported with relatively great frequency in this group. In our series coma was a common complication One patient had tuberculosis, hepatomegaly and dwarfism

The management of the diabetic child under age three may be perplexing to the family and dietary and insulin discipline may be difficult indeed. Actually, the diet of the normal child of this age is quite suitable for the diabetic, and 3 to 6 small meals may be planned including the following foods 1 quart of milk, 1 egg, 15 grams of butter, 15 grams of cereal, 60 grams of bread, 60 of potato, 15 of bacon, 75 of meat, 200 of vegetables, 300 grams of [illegible]

[illegible] cepts the hypodermic injection of insulin, in the home the very young patient protests and may hide in a convenient closet or under a sheltering bed.

[16] Lamper and Miller Am Jour Dis Child, *50*, 1216, 1935, Newcomb and Farrell Ibid, *81*, 302, 1951, Brodribb, McMurray and Scott Brit Med Jour, *1*, 1060, 1952

The rush of the morning does not soften the attitude of the family toward the young rebel who is often caught and chastized. The administration of insulin then becomes punitive with tension built up between child and parent. The importance of patience and sympathy cannot be overemphasized in this respect.

The choice of insulin for the very young child is important. At this age the child's relative requirement for rapidly acting insulins is great. Although long-acting insulins are desirable in the treatment of diabetes, some have favored CI or RI at six-hour intervals for the early years. Separate injections of CI and PZI in almost equal doses give satisfactory results. With NPH a mid-morning reaction may be encountered and it may be necessary to anticipate this with extra carbohydrate in the mid-morning or for breakfast.

The interpretation of tests for glucose are most difficult because the volume of urine is small and a maximum reduction may measure but a gram or two in this age group. Quantitative determinations for glucose are desirable. These tests can be done with simple testing sets such as the Clinitest. A simple spot test for acetone should be made daily.

To recapitulate our previous statements for emphasis, younger children

Such infections may precipitate acidosis, indicated by the purple color of the test for acetone, suggested by the development of thirst, nausea, vomiting, pauseless breathing and drowsiness. Supplementary doses of insulin, 4 to 6 units, at three-hour intervals based on poor tests should prevent acidosis.

juice will relieve the symptoms quickly. Parents should be taught to administer 0.3 cc. of adrenalin chloride if the child cannot swallow.

Growth and development and progress in school can be expected to follow normal patterns.

Daily tests for sugar should be done. The pre-breakfast test guides the changes in long-acting insulin. The pre-lunch test guides the changes in rapidly-acting insulin. Medical checkups are desirable at three-month intervals. Yearly readjustment of treatment in the camp or hospital is recommended.

X. COMPLICATIONS OF JUVENILE DIABETES

The relative frequency of the complications of childhood diabetes varies with the duration of the disease. Thus, in the first five years of diabetes the following occur most commonly: ketosis, sepsis, cataracts, hepatomegaly and the three skin lesions, xanthosis, necrobiosis lipoidica diabeticorum and xanthoma diabeticorum. Between the fifth and the fifteenth year are seen the neuropathies and after 15 years the vascular lesions appear.

Diabetic Coma.—In juveniles the incidence of diabetic coma is relatively great. Yearly, 40 per cent of the coma admissions of the Joslin Clinic are childhood diabetics, although the children comprise but 10 per cent of all of our patients. The intercurrence of infections, omission of insulin and overeating are the inciting causes. Similar irregularities in the diabetic adult do not precipitate coma as easily as they do in the child. Upon a quantitative basis *the adult has greater stores of protective glycogen.* The child's deficiency of glycogen has been demonstrated experimentally by Mirsky and Nelson,[19] who administered phlorhizin, 15 to 20 grams, to diabetic children and produced hypoglycemia and ketonuria. This did not occur in the adult.

The incidence of severe ketoacidosis in juveniles with many possible years of exposure was measured in 1072 of our children who in January 1956, had survived 20 or more years of diabetes. It was 52 per cent for [illegible]

abdominal pain and [illegible]

[illegible] of insulin, . . . patients whose reserve fell to this level recovered. In the juvenile population those who are most susceptible to coma are the adolescents, comprising 80 per cent, females 66 per cent, short duration cases, under 5 years, 44 per cent. [illegible]

normal or low magnesium, elevated leucocytosis and increased excretion of oxysteroids. The urine contains sugar, acetone, albumin and casts. The level for acetone in the serum is high.

The objectives of treatment become correction of metabolic upheaval and include (1) al[illegible] glycogen, (3) [illegible] $BHCO_3$, and [illegible] each objective, its action must be supplemented with other measures.

Insulin Treatment.—The age of the patient is frequently a guide for the dose of insulin to be employed. Thus, the average dose in the first 24 hours [illegible]

[19] Mirsky and Nelson: Jour. Am. Med. Assn., 67, 100, 1944.

sugar was between 500 and 750 mg., the dose of insulin was 250 units, and when the blood sugar was between 750 and 1000 mg., the average dose for these patients was 500 units. As the severity of coma becomes more marked, as measured by the state of consciousness, the intravenous administration of insulin should be combined with the subcutaneous administration and the frequency of the dose increased to half hour intervals. The percentage of t[illegible]
Thus, regardl[illegible]
50 per cent of [illegible]
hours to come. However, the dangers of overtreatment are far less than the dangers of undertreatment.

Hydration is gauged by the volume of the urinary output It is considered adequate when the output is 50 cc. per hour. Normal saline appears to be effective for most cases.

For electrolyte repair, potassium is used if the blood level falls below 3mEq., electrocardiographic changes occur, gastric dilation persists or the clinical picture of flaccidity and respiratory failure develop.

Sodium lactate ($\frac{1}{6}$ *M*) is used, *especially* if nephritis complicates ketoacidosis. Hartmann[39a] uses sodium lactate 60 to 90 cc. per kg. and Ringers solution 40 cc./kg. Guest[39b] favors bicarbonate and Butler[39c] recommends the multiple hypotonic electrolyte solution of Talbot and Crawford, 3 5 liters per square meter. This solution contains per liter na 40 m/Eq., k 35.5 m/Eq., cl. 40 m/Eq., lactate 20 m/Eq., phosphorus 15 m/Eq., and [illegible] Thorn and Forsham[39d] recommend adding 500 cc.
[illegible]
kalemia potassium hydrogen phosphate, 2 gm. potassium dehydrogen phosphate, 0.4 gm., distilled water to 50 cc added to a liter of the solution used

Glucose is used only if the level of blood glucose is low, since its use favors water intoxication and hypokalemia. Carbohydrate as orange, oatmeal or milk, 5 grams per hour, is given when vomiting is controlled; antibiotics are often necessary Shock may be treated with nor-epinephrine *and hypochloremic anuria with 10 per cent salt solution.* Unless the patient is in marked shock, gastric lavage should be a routine procedure. In spite of restlessness and obvious pain, opiates and sedatives should be avoided During convalescence the first day's diet consists of a soft solid diet of 150 grams carbohydrate, 50 of protein and 50 of fat

Differential Diabetic Diagnosis.—In the juvenile patient the following must be differentiated from ketoacidosis: surgical abdomen coexistent with ketoacidosis, uremia, diphtheria, pneumonia, hypoglycemia, salicylic [illegible] hypo- [illegible] umonia, urinary tract infection, arterial thromboses and infections.

[39a]Hartman Loc cit p 370
[39b]Guest Loc cit p 370
[39c]Butler Loc cit p 370
[39d]Forsham and Thorne Loc cit p 645

Prevention of ketoacidosis should be taught by careful chemical control. Thus, parents can be taught a quantitative determination of sugar for the 24-hour period, daily qualitative tests, spot test for acetone, the daily

the cure for tomorrow "

Prognosis.—Among childhood cases of coma at the Joslin Clinic, the case recovery was 98 per cent and the patient recovery 97 per cent There were no deaths under age 10, two under age 15. Multiple attacks of diabetic coma are undesirable Twenty-six of our juvenile patients had from three to ten attacks The *subsequent course of the juveniles who had experienced* diabetic coma showed the following: tuberculosis in 5 per cent, retinopathy in 25 per cent, nephropathy in 20 per cent *Seventy-five per cent were alive* at the time of the most recent follow-up

and terminate fatally Delayed development of antibody to staphylococcus toxin in diabetic children was observed by Bates and Weiss,[40] who compared 14 normal children with diabetics given 7 or 8 weekly injections of

slower production of alpha antistaphylolysin, but the maximum titers attained after several weeks of immunization were lower than those of a similar group of normal children Lack of control of diabetes retarded and diminished the production of antihemolysin

The most frequent infections are those of the skin and of the urinary tract

hood

in 1072

33, 12 and 0 5 per cent for females

Tuberculosis —In the association of the two diseases diabetes and tuberculosis, diabetes increases susceptibility to tuberculosis but tuberculosis does not increase susceptibility to diabetes In our juvenile population diabetes antedated tuberculosis in all cases

The incidence of tuberculosis in juvenile diabetes was 12 times and in adolescent diabetes was 20 times that of the general population. Among 1072 twenty-year survivors the incidence of tuberculosis was 4 per cent.

ity

age

22 per cent between 15 0 and 19 9 years. Acquired immunity gave no protection Forty-two

bronchial adenitis

coma This is not

[40] Bates and Weiss Am Jour Dis Child, 62, 341, 1941

dehydration occurs and when the pH is between 6.4 and 7.8. Growth is further favored by protein catabolites and by glucose. Its virulence is increased in acid media and phagocytosis is interfered with when fat is stored in excess in the reticuloendothelial system.

The rules for the management of infections in diabetes are the same as those for the general population. However, Staphylococcus albus is more often pathogenic. Simple therapeutic rules are as follows: penicillin for gram positive; erythromycin for resistant gram positive cocci; gantrisin for gram negative organism; streptomycin for resistant gram negative organism; for marked resistance, the combination of aureomycin, terramycin and chloromycetin.

Cataracts.—Cataracts have been identified in 1.5 per cent of our juvenile diabetics. Not all of the children have been examined routinely with the slit lamp. Most of these cataracts occur early in the course of the disease, even at the time of the diagnosis of diabetes; often they are observed in patients whose disease is under three years' duration and are rarely first diagnosed after five years of diabetes. Opacities in the posterior subcapsular area and showers of fine cholesterol crystals can be demonstrated. Not all progress The treatment is surgical when the vision is sufficiently impaired

O'Brien[41] reports cataracts in 14 per cent of 260 cases examined Wachs[42] reports reversal of the cataract, a case in a 16-year-old diabetic; Boyd, Jackson and Allen[43] report posterior subcapsular opacities in one-third of 69 diabetics related to episodes of poor control of diabetes. In contrast to this latter view, Karlstrom[44] reports 38 children treated with the free diet without cataracts

Our own experience with these patients who have developed cataracts correlates them with poor control of the disease. A common history is of unrecognized diabetes, active symptoms of diabetes for a year, recognition of diabetes n coma and signs of vitamin B deficiency. Recently it has become apparent that after twenty years of diabetes, susceptibility to senile cataract formation occurs

Hepatomegaly.—Hepatomegaly was seen commonly in the juvenile diabetic before the use of long-acting insulins The livers were so large they frequently extended into the true pelvis and contained large quantities of lipid material However, as biopsies were done mostly on patients prepared for a surgical procedure, biopsy results have frequently shown the presence of glycogen and fat in quantities greate than normal. Tests for liver function are invariably normal Long-acting and intermediate insulins prevent and correct this complication

Xanthosis Diabeticorum—Xanthosis diabeticorum has been common in juveniles because they select the vegetables high in carotene, carrots, peas and tomatoes being the favorite three Due to the large liver the diagnosis

[41] O'Brien and Allen Jour Am Med Assn, *120*, 190, 1942
[42] Wachs Am Jour. Ophth, *25*, 336, 1942
[43] Boyd, Jackson and Allen Jour Am Med Assn, *118*, 694, 1942
[44] Karlstrom Sveno Ratak Tidning, 38, 2623, 1941

rapidly acting insulin, the control of fat metabolism was more difficult. Today, these lesions are exceptional

Necrobiosis lipoidica diabeticorum occurs in 1 out of every 50 juveniles in contrast to 1 in 400 adults. Fifty per cent of all our cases had onset of diabetes in childhood. Females predominate, accounting for two-thirds of the cases. The lesions are recognized sometimes at diagnosis of diabetes Their natural course includes a macular stage, plaque, ulcer and finally, a scar The tendency toward spontaneous recovery appears to be acceler-

neuropathy. Growth failure was seen more commonly in the young diabetic male than in the young diabetic female, and the incidence was formerly as high as [illegible]
have all

Dwarfi

more inches below the standard of Baldwin and Wood were reported by Wagner, White and Bogan.[45] The child most susceptible to retardation was the one whose age at onset of diabetes occurred under five years. Boys, *constituting 92 of the total,* were *more susceptible than girls.* Although at onset of retardation the child is often of subnormal weight, eventually obesity occurs One child was 4 inches below normal height at onset

[illegible]

[illegible] low calcium in 2 of 11 cases and low phosphorus in 3 of 17 tested Cataracts, infect[illegible]

as possible causes of retardation. [illegible]
not favor the theory that undernut[illegible]

[illegible]

ties who had distended abdomens and infantile primary and secondary sex organs Miller and Mason[47] have observed diminished excretion of 17-ketosteroids in retarded diabetic children

The therapy of diabetic pseudodwarfism in our patients has passed

[45] Wagner, White and Bogan Loc. cit. p 661
[46] Chesler and Tislowitz Science, *101*, 468, 1945
[47] Miller and Mason Jour Clin Endocrinol, 5, 220, 1945

through four stages: dietary, thyroid, anterior pituitary extract and sex hormones. Dietary treatment was difficult because these children have small appetites. Thyroid feeding was followed by growth in some, but not all cases. Presumably it resulted from stimulation of the eosinophilic cells of the pituitary as in the congenital dwarf mouse so treated. Good results were obtained when pituitary extracts were administered intramuscularly with or without thyroid. So long as the epiphyses were open, response occurred at any age, but after seventeen years of age, puberty was precipitated and the period of gro

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formula all show that accelerated growth followed the administration of anterior pituitary extract.

The greatest acceleration of growth followed the use of testosterone in retarded boys. Masculinization followed its use in girls who responded somewhat to estrogen therapy. The usual prescription was Oreton 25 milligrams intramuscularly twice or three times weekly for two or three years. ACTH has been recommended but has not been used in our patients.

The criteria for selection of cases for treatment is bone age of two years or more, less than the chronological, open epiphyses, height 4 or more inches below the standard for age. The diet for the retarded group must be adequate in calories and high in protein, 2 grams per kilogram of body weight supplemented with vitamains.

No harmful growth effects were observed. There was no evidence of antihormone production. The probable effect upon the course of diabetes is of interest. Measured by units of insulin per kilogram, the retarded child treated with growth promoting substances has the greatest requirement of any group studied; namely, tall children, ten-year duration children, untreated dwarfs and thyroid-treated dwarfs. No attacks of coma were precipitated.

Nutritional rather than an endocrine origin is the view of McCullagh,[474] and Herron and Shepardson.[475] Isolated reports of dwarfism have been made by Villanerde[476] and Oakley.[476]

Failure of growth, like hepatomegaly, has disappeared with the use of

betics between the ages of 10 and 20 showed diminution in the upper extremities in 40 per cent and in the lower extremities in 70 per cent.

Among 1072 twenty-year survivors, neuropathy had occurred in 26 per cent of the females and 20 per cent of the males. Acroneuritis was the form observed most commonly, with gastrointestinal neuropathies in second place. Such malignant neuropathies as Argyll-Robertson pupils,

[474] McCullagh. Rev. Psychiat., Progress Related to the Exceptional Child, p. 49, 1944.

tabetic bladders, and Charcot joints occurred infrequently, in only 0 3, 0 3 and 0 5 per cent respectively

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all been disappointing.
igated
and mortality, vascular damage is by far the most important complication. In their later lives at 35 years' duration nearly all juvenile diabetics show lesions; 94 per cent

first ten years, but by fifteen years, 19 per cent of those examined had retinopathy, 14 per cent calcified arteries, 7 per cent proteinuria, 4 5 per cent hypertension, and 3 per cent proliferans

TABLE 127 —TOTAL INCIDENCE OF VASCULAR LESIONS BY DURATION AMONG 1072 CASES

Duration years	*Albumin per cent*	*Blood pressure per cent*	*Retinitis per cent*	*Retinitis proliferans per cent*	*Calcified arteries per cent*
0–4	0 8	0 5	0	0	0
5 9	1 5	1 2	2 5	0	1 7
10–14	7	4 5	19	3	14
15–19	18	15	59	18	44
20–24	41	32	82	47	73
25–29	39	44	88	46	88
30–34	44	53	93	59	94
35–39	63	70			

63 per
etinitis

TABLE 128 —TOTAL INCIDENCE OF VASCULAR LESIONS BY AGE AMONG 1072 CASES

Age Years	*Albumin per cent*	*Blood pressure per cent*	*Retinitis all types per cent*	*Retinitis proliferans per cent*	*Calcified arteries per cent*
0 9	0	0	0	0	0
10 19	4 2	1 8	4 8	0	6 5
20 29	18 5	16 7	63 2	28 7	45 5
30 39	34 7	40 3	84 4	53 1	83 3
40 49	37	51 9	88 0	58 4	95 0
50+					

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in 2 and gangrene in 0 5 per cent), there is increasing evidence that certain numbers of these patients show a stationary status of their vascular lesions. This favorable course can be evaluated best in the retina

through four stages: dietary, thyroid, anterior pituitary extract and sex hormones Dietary treatment was difficult because these children have small appetites. Thyroid feeding was followed by growth in some, but not all cases. Presumably it resulted from stimulation of the eosinophilic cells of the pituitary as in the congenital dwarf mouse so treated Good results were obtained when pituitary extracts were administered intramuscularly with or without thyroid. So long as the epiphyses were open, response occurred at any age, but after seventeen years of age, puberty was precipitated and the period of growth shortened, resulting in an adult who still had infantile proportions. Puberty was not precipitated in the younger cases and the end result is one of more proportionate growth. The growth curve, the yearly percentage rate, and the velocity measured by Broca's formula all show that accelerated growth followed the administration of anterior pituitary extract

The greatest acceleration of growth followed the use of testosterone in retarded boys. Masculinization followed its use in girls who responded somewhat to estrogen therapy. The usual prescription was Oreton 25 milligrams intramuscularly twice or three times weekly for two or three years ACTH has been recommended but has not been used in our patients

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[illegible] ine origin is the view of McCullagh,[47a] an [illegible] lated reports of dwarfism have been m[illegible]

Failure of growth, like hepatomegaly, has disappeared with the use of long-acting insulins

Neuropathy.—Short bouts of peripheral neuritis occur in younger diabetic children *Danowski*[48] *measured the vibratory sense and found that diabetics between the ages of 10 and 20 showed diminution in the upper* extremities in 40 per cent and in the lower extremities in 70 per cent

Among 1072 twenty-year survivors, neuropathy had occurred in 26 per cent of the females and 20 per cent of the males Acroneuritis was the form observed most commonly, with gastrointestinal neuropathies in second place Such malignant neuropathies as Argyll-Robertson pupils,

[47a] McCullagh Rev Psychiat, Progress Related to the Exceptional Child, p 49, 1944

[47b] Herron and Shepardson Clinics, *1*, 782, 1942

[47c] Villanerde Vida Nueva, *18*, 42, 1944

[47d] Oakley Proc Royal Soc Med, *35*, 450, 1942

[48] Danowski Loc cit, p 659

observed at the microscopic level in the bulbar conjunctiva. Such examinations have been made upon this group by Ditzel[19] and have shown two types of patterns. One is characterized by the loss of venular tone and by venular dilatation The second is characterized by increased arteriolar constriction The changes are followed by intravascular aggregation of erythrocytes, by perivascular edema and by hyaline deposition Long-term

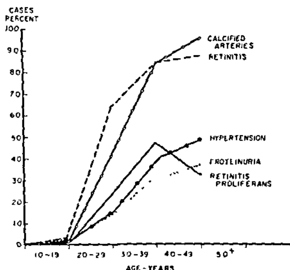


Fig 36

diabetics show these abnormal responses, and untreated and uncontrolled cases to an exaggerated degree It is significant that these changes were also observed in children of diabetic mothers, 16 per cent in those with normal glycemia, 51 per cent in those with hyperglycemia

Retinopathy.—The earliest of the vascular lesions to be recognized clinically in the juvenile patient is retinopathy In the juvenile patient, marked changes occur in the capillary venule and arteriole The capillary changes include microaneurysms looping and new formation Seen almost simultaneously is the earliest of the venular changes, dilatation and darkened color [illegible]

[19] Ditzel and White Loc cit, p 413

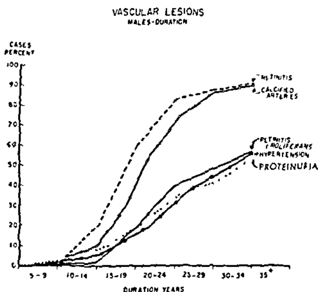


Fig 34

AGE AND VASCULAR LESIONS
MALE

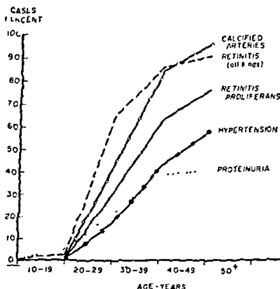


Fig 35

All blood vessels of these young patients are involved in all types of sclerosing processes, but the significant, progressive and lethal lesions involve the arterioles, capillaries and venules. These small vessels can be observed at the microscopic level in the bulbar conjunctiva. Such examinations have been made upon this group by Ditzel[49] and have shown two types of patterns. One is characterized by the loss of venular tone and by venular dilatation. The second is characterized by increased arteriolar constriction. The changes are followed by intravascular aggregation of erythrocytes, by perivascular edema and by hyaline deposition. Long-term

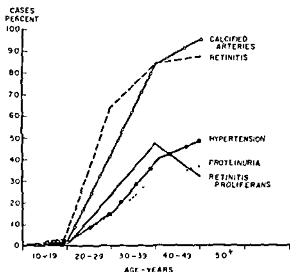


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Retinopathy.—The earliest of the vascular lesions to be recognized clinically in the juvenile patient is retinopathy. In the juvenile patient, *marked changes occur in the capillary, venule and arteriole.* The capillary changes include microaneurysms, looping and new formation. Seen almost simultaneously is the earliest of the venular changes, dilatation and darker [illegible]

In [illegible]

are ev [illegible]

[49] Ditzel and White. Loc. cit., p. 413

ones. Sheathing of vessels may be evident and hemorrhages of many types, punctate, small round, blotchy, pre-retinal, vitreous and at any time superimposed renal nerve-fibre or striate.

Exudate at first is punctate; the waxy character is clearer as the lesion increases in size, and suggests coalescence Cotton-wool exudate may be superimposed. The exudate is sometimes white, at other times this may appear yellow when histologically leucocytes with lipid material occur. D[illegible]

DBI are used therapeutically as well as medical hypophysectomy (progesterone) and medical adrenalectomy (cortisone).

[illegible]

retinopathy usually precedes protinuria Soon renal retinopathy appears. Proteinuria occurs rarely before the fifteenth year of diabetes and rarely before twenty years of age. Edema develops gradually as does hypertension which is usually of moderate degree. The total protein falls, the A/G ratio is reversed, the cholesterol levels increase and lipoprotein in the SF 12:20 range increases. The urine contains doubly refractile bodies but few cells or casts. Anemia becomes progressively severe, renal acidosis is common; low salt syndrome develops, congestive heart failure occurs; distressing encephalopathies intervene and uremia is almost inevitable. Management is discussed on pages 429–432

Calcification.—Calcification of arteries is the second most common vascular lesion in juvenile diabetes Between the fifteenth and nineteenth years of the disease, 25 to 35 per cent of carefully studied juveniles show this lesion It has not been observed under ten years of age or prior to the fifth year of diabetes The youngest patient in our group to show the lesion was eleven years of age The shortest duration occurred in two cases, both of whom showed calcification by *x*-ray at eight years' duration

Following the areas of lowest vascular reserve the lesion appears first in the ankle, then the leg, pelvis and abdominal aorta Lichtenstein[50] believes patients treated with higher carbohydrate diets do not tend to develop this lesion Such has not been our experience

Gangrene is an infrequent complication in diabetes with onset in childhood

The search for the cause and the means to prevent vascular lesions has, therefore, become the main objective in the management of juvenile diabetic patients That extreme degrees of poor control precipitate these vascular lesions all agree, the extreme degree of poor control being ketoacidosis, but that good control protects the patient from vascular damage is a debated point The data of a series of our young long-term diabetics evaluated for control and vascular lesions by incidence and intensity has been reported by Keiding, Root and Marble[51] One hundred eighty-nine

[50] Lichtenstein Proc Internat Cong Pediat, Zurich, Switzerland, 1950
[51] Keiding, Root and Marble Loc cit, p 409

cases were evaluated after 20 years of diabetes. When control was graded excellent to good (32 cases) grade 3 or 4 retinopathy was found in 3 per cent only, but when it was fair to poor (157 cases) 31 per cent were found to have severe degrees of retinopathy (Table 129)

TABLE 129.—RETINOPATHY AND CONTROL AFTER 20 YEARS' DURATION IN 189 CASES

Control	*No*	*Retinopathy Grades 3 and 4 (Per Cent)*
Excellent to good	32	3
Fair to poor	157	31

TABLE 130.—NEPHROPATHY AND CONTROL IN 451 CASES OF YOUNG DIABETICS

Control	*No*	*Nephropathy Per Cent*
Excellent	11	0
Good	50	2
Fair	92	17
Poor	298	28

Four hundred fifty-one cases of suitable duration, 10 to 36 years, were graded and evaluated for nephropathy Nephropathy did not occur in the eleven with excellent control, in 2 per cent of those with good control (50 cases), in 17 per cent of 92 cases with fair control but in 28 per cent of 298 cases with poor control (Table 130) The conditioning of vascular damage by poor chemical control has been reconfirmed in 1954 by Dunlop [52] Using the alternate case study method, free diet and no chemical control, restricted diet and chemical control, he found such rapid precipitation and progression of vascular lesions in patients using the free diet and having no chemical control that he abandoned his experiment Engleson,[53] studying those patients in Sweden in whom this free type of management was first applied, came to similar conclusions

In order to learn more about vascular response and degeneration a study of the small blood vessels at the microscopic level has been made upon our juvenile diabetics by Dr Jørn Ditzel [54] He selected the conjunctiva as the object of study because this is the only area of the body where arterioles, venules and capillaries can all be visualized *in vivo* One hundred forty children were examined He found in the vascular pattern of 70 "healthy" children that the *arterioles* entered the conjunctiva parallel to the venules They branched and gave rise to terminal arterioles *Capillaries* branched from arterioles and their network appeared regular and ordered No angulations, tortuosities or localized sacculations were found *Venules* were smooth with an A V ratio of 1 3 to 1 2 There was no extravascular edema or

[52] Dunlop Loc cit p 425
[53] Engleson Loc cit p 421
[54] Ditzel Circulation, *14*, 386, 1956

ones. Sheathing of vessels may be evident and hemorrhages of many types, punctate, small round, blotchy, pre-retinal, vitreous and at any time superimposed renal nerve-fibre or striate

Exudate at first is punctate; the waxy character is clearer as the lesion increases in size, and suggests coalescence. Cotton-wool exudate may be superimposed. The exudate is sometimes white, at other times this may appear yellow when histologically leucocytes with lipid material occur. Dense white scars traverse the retina, leading to separation.

Hemorrhagic glaucoma may intervene and phthisis of the bulba result

Good chemical control is stressed in prevention. Currently CVP and *DBI* are used therapeutically as well as medical hypophysectomy (pro- [illegible]

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[40] Lichtenstein Proc Internat Cong Pediat, Zurich, Switzerland, 1950
[41] Keiding, Root and Marble Loc cit, p 109

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restricted diet and chemical control, he found such rapid precipitation and [illegible]

applied, came to similar conclusions

In order to learn more about vascular response and degeneration a study of the small blood vessels at the microscopic level has been made upon our juvenile diabetics by Dr Jørn Ditzel[14] He selected the conjunctiva as the object of study because this is the only area of the body where arterioles, venules and capillaries can all be visualized *in vivo* One hundred forty children were examined He found in the vascular pattern of 70 "healthy" children that the *arterioles* entered the conjunctiva parallel to the venules They branched and gave rise to terminal arterioles *Capillaries* branched from arterioles and their network appeared regular and ordered No angulations, tortuosities or localized sacculations were found *Venules* were smooth with an A V ratio of 1 3 to 1 2 There was no extravascular edema or

[12] Dunlop Loc cit p 425
[13] Engleson Loc cit p 424
[14] Ditzel Circulation, *14*, 386, 1956

hyalinization. The 70 diabetic children studied had been diabetic from six months to thirteen years and their ages at the time of the study ranged from six to eighteen years. Three distinct types of patterns were observed In addition to the normal pattern was a group designated as vascular pattern-change I and a group complex designated as vascular pattern-change II. Ten per cent of the children at the time of the examination showed the normal pattern, 81 per cent vascular pattern-change I, and 9 per cent vascular pattern-change II. No child whose duration of diabetes was less than 5 years exhibited vascular pattern-change II.

Certain fundamental similarities and differences in conjunctival and retinal vessels clarify possible mechanisms and probable relations to diabetes control The similarities between the conjunctiva and the retina are many In both tissues the only vessels present are arterioles, capillaries and venules The responses to stimuli are identical—vascular dilatation, perivascular edema, hyalinization and intravascular aggregation of red blood cells In both the rate of blood flow becomes impaired leading to stasis and finally to varying degrees of hypoxia and starvation In contrast to the conjunctival vessels, the retinal vessels have a basement membrane. The retinal lymphatic supply is poor whereas lymphatic network of the conjunctiva is rich The metabolic needs of the retina are great, of the conjunctiva little The capacity for prolonged adaptation in the conjunctiva is high, in the retina low The conjunctival responses are reversible for a long time, the retinal for a limited time. The venous vascular responses are the first and most easily recognized in the conjunctiva. These responses cannot be observed in the retina because of the limitation of the magnifying power of the ophthalmoscope Due to differences in functional need, venules are affected in the conjunctiva whereas capillaries and venules both are affected in the retina (Table 131)

TABLE 131 — VASCULAR RESPONSE IN CONJUNCTIVAL VESSELS JUVENILE DIABETES

Pattern I	*Pattern II*
Vascular Arteriolar constriction Venular distension and darkening color A V Ratio 1 3I 10 Capillary irregularities	Vascular Marked arteriolar constriction Capillary closure Venular narrowing
Perivascular Edema Hyaline infiltration	Perivascular Edema Hyaline infiltration
Intravascular Aggregation of RBC	Intravascular Aggregation of RBC

Thus for a long period of time the conjunctival responses are reversible in part or whole, whereas the retinal responses may be reconstructed as follows: arteriolar constriction, capillary narrowing, venular distension and narrowing leading to aggregation of red blood cells, stasis, hypoxia and starvation and to exudation. Eventually, hyalinization of the basement membrane occurs. Microcapillary aneurysms result. Proliferation of new

Table 131

The affectors of vascular responses are many. Constriction follows increased O_2 tension, decreased CO_2 tension, ACTH and cortisone. Stress, infection, hypoglycemia, ketoacidosis and pregnancy, associated with increased adrenal steroid hormone production may be factors in diabetic microangiopathy. The experiments of Friedenwald and Becker[54a] and of Hamwi[55] and co-workers suggest that cortisone or ACTH may produce int … imal

The

res … ors of constriction include oxygen of low tension, CO_2 of high tension, and increase in the pH. Factors favoring intravascular aggregation include glucose and beta-lipoproteins

but also suggests programs for prevention and treatment.

O DISEASES OF THE OTHER ENDOCRINE GLANDS AND DIABETES

pituitrin

Adrenal.—The endocrine gland which is third in rank in connection with carbohydrate metabolism is the adrenal. Marked clinical evidence … our children. Truly … One of our dwarfish … ketosteroid excretion … characteristic of diabetes at onset followed by subnormal levels in many cases after ten years' duration of the disease. One child has proven Addison's disease (Case 22770)

Thyroid.—The incidence of thyroid disease in juvenile diabetes is somewhat coincidental. Thus among 3144 children there have been 5

[54a] Becker: Editorial, Diabetes, 5, 151, 1956

[55] Hamwi: Ibid., p. 37

cases with typical primary hyperthyroidism (Cases, 377, 3428, 10713, 14148, 27590). There was nothing remarkable about them. Diabetes was aggravated until the patients were relieved of their hyperthyroidism by operation. Five of our children have been treated for hypothyroidism (Cases 5560, 14850, 21367, 20473, 22617).

Gonads.—The role of the gonads in diabetes is of interest because of the possible etiological relationship—the greatest incidence of onset occurring at twelve years of age, and the effect of catamenia on the course of the disease Removal of the gonads does not prevent the onset of diabetes in the depancreatized animal. An increased sensitivity and finally increased [illegible]

and twenty-one days. Blood-sugar determinations were not made. Whether this is a change in severity or threshold, we do not know.

TABLE 132 —FSH AND 17-KETOSTEROID VALUES IN HYPO-MENORRHEIC DIABETIC GIRLS

Age	*Case No*	*17-Keto-steroid*	*FSH M U /100 cc Serum*	*Menses*
18	21516	0 32	+33	Amenorrhea 3 years' duration
28	11032	0 36	<33	Irregular amenorrhea—long periods
32	20814	1 60	+*	Irregular
14	21060	1 60	<33	Not established
20	10628	2 30		Irregular, every 6 weeks
14	12824	2 40		Not established
18	20358	2.60	+*	Amenorrhea
18	27888	2 90	<33	Irregular
18	18935	3 00	<33	Amenorrhea
22	20332	3 50	+33	Amenorrhea
22	21586	3 70	N D	Amenorrhea
18	11420	3 70	+33	Irregular
19	16332	3 80	+50	Amenorrhea
20	24626	4 20	<33	Onset 18—every 4 months
28	27467	4 40	+33	Regular

* Urine 20 milligrams

Low level of 17-ketosteroid in diabetic boys and young male adults suggests hypogonadism after years of duration of the disease The levels fall below that which might indicate adrenal insufficiency alone.

Amenorrhea, meno- and metrorrhagias and chronic cystic mastitis complicate diabetes A syndrome of edema, amenorrhea accompanied by low level of 17-ketosteroid excretion and often with high level of FSH, has been observed in 22 of our diabetic girls. This probably represents the earliest clinical stage of diabetic nephropathy.

Amenorrhea in this group is corrected, but presumably with anovulatory cycles, by the administration of stilbesterol 0 5 milligrams daily for fourteen days followed by the administration of pranone 10 milligrams daily for seven days and omission of therapy for seven days. Thyroid, 1 grain of Armour's extract, is given continuously, but thyroid alone has rarely

corrected amenorrhea in this group If the 17-ketosteroid excretion is low, the hypogonadism in boys has been treated with testosterone.

Su

hypothalamic deficiency has been suspected.

F. PROGNOSIS

Twelve hundred twenty-eight, or 30.3 per cent, of our 4054 cases had survived twenty or more years of diabetes up to January 1957. Sixty, or 5 per cent survived more than 35 years; 247, or 6 1 per cent survived over 30 years, 735, or 18 1 per cent survived 25 years

The estimated expectation of life is three-fourths that of the normal

Achievements.—Among the 1072 twenty-year survivors the struggle to survive and to achieve, even after the development of multiple disabilities is amazing. A famous case of pituitary dwarfism, reported by Beck and

A

did

ccu-

for

urban populations for males Those in professions, 26 per cent, exceeded the number expected in the general population, 6 per cent, by more than four times, as follows

	Expected Per Cent	*Actual Per Cent*
Professional	6	26 3
Semiprofessional	13	18 1
Clerical	29	22 7
Farmers	0 4	2 3
Semiskilled	29	16 8
Slightly skilled	13	6 9
Day labor	8	5 3

Mortality.—Cardiorenalvascular lesions have replaced nearly all other causes of death The changing status with respect to causes of death is shown by the near disappearance of coma, sepsis and tuberculosis, formerly the chief causes of death.

Summary.—The predisposition to diabetes in childhood is hereditary. The disease follows a natural course

sion to a total

resolved them

coma, sepsis a

replaced other

an important factor contributing to vascular damage Present forms of available insulins control diabetes with greater facility than those used formerly, and programs to alter the course of diabetes, especially those applicable in the remission phase, are in progress

[66] Beck and Suter Endocrinology, 22, 115, 1938

[67] Gesell, Ilg and Ames Youth—The Years from Ten to Sixteen, New York, Harper Bros, 1956

Chapter 28

PREGNANCY COMPLICATING DIABETES

PRISCILLA WHITE, M.D.

A. INTRODUCTION

THE management of the obstetrical patient in the Joslin Clinic has developed from a concept of the natural course of pregnancy in diabetes, an evaluation of the factors which contribute to the natural course, and comparison of the results of three different types of management used by us as well as by others

B. MAGNITUDE OF THE PROBLEM OF OBSTETRICAL DIABETES

It is estimated that there are some 80,000 diabetic women of childbearing age in the United States Fifty thousand former juvenile diabetics are or soon will be potentially childbearing. These patients are concerned with their chances for (1) conception, (2) for surviving pregnancy, (3) for increasing the severity of their disease, (4) for increasing the hazards of the com-

ined at the Joslin Clinic since 1898. Determinations for one or more of the female sex hormones have been made on some 1200 of these, 1028 reached the viable period of 28 weeks, and form the group of our reported series

Natural Course.—The natural course of pregnancy in diabetes may be summaraized in a single word, destruction. This destructive tendency was shown strikingly in the preinsulin era, when few diabetic women conceived and the few who conceived rarely survived pregnancy, succumbing *undelivered to ketoacidosis*

The natural course of pregnancy in diabetes even in the insulin era can be summarized in the word destruction, but destruction in part only

partum and neonatal deaths is 45 per cent, previable losses are 20 per cent, toxemia incidence 33 per cent, and some degree of hydramnios is present in all *Contrast this with normal, obstetrical experience where the perinatal* loss is 3 per cent, previable losses 10 per cent, toxemia incidence 3 per cent and hydramnios is absent except when twin pregnancies or multiple births occur

found in all three The positive correlation between fetal loss and abnormalities is undoubted in some, probable in others, possible but not proved in some

C. MATERNAL FACTORS INFLUENCING NATURAL COURSE

be

may exist for long periods during pregnancy and exert harmful influences In our own series of cases the CO_2 content of the blood fell to 9 m/Eq or below during pregnancy in 21 diabetic women and the fetal mortality in

pregnancy, increases abnor-
pregnancies reaches levels
inferred from erythrocyte

betalipoprotein, however, is often short but its occurrence is frequent To evaluate the possible prenatal harmful influence, the average third trimester blood sugars of the women whose infants survived was compared with those whose infants had not survived and the values were 160 and 165 mgs. respectively, almost identical These values were postprandial and total reducing substance

Fetal loss is sometimes attributed to hypoglycemia.

had toxemia and was in the thirty-first week of pregnancy In spite of continuous administration of glucose she became hypoglycemic to the point of unconsciousness but was delivered of a healthy infant six weeks later Another patient in the twelfth week of pregnancy, Case 3040, was

survival of the infant

Whether or not the placenta is permeable to insulin has not been clearly

established. *Snyder and Hoskins*[1] *presented evidence of failure of the passage of insulin from fetal to maternal circulation.* Britton[2] showed that the administration of insulin to pregnant cats failed to reduce the blood sugar level of the fetuses near term. A species difference in fetal resistance to insulin is shown by the experiment of Schlossmann and Parsmore.[2a] *The fetal dog, sheep and goat are resistant to insulin, the latter two scarcely* responding to doses as great as 415 units per kilogram of weight (administered directly into the fetus). In contrast to these animals, fetal rats are susceptibile even when insulin is injected into the mother Although the placenta plays an important role in fetal glycogen metabolism, the fetal *liver can function Since the fetus is not diabetic its liver should respond* to the stress and strain produced by placental glycopenia. Our clinical experience does not favor the theory that the disordered carbohydrate metabolism of uncontrolled diabetes or hypoglycemia *per se* causes many of the fetal deaths

The influence of structural changes upon fetal loss cannot be doubted. Two structural changes have been recognized and described. They are vascular damage and uterine hypoplasia. Uterine hypoplasia characterizes diabetic dwarfism Failure of the uterus to expand is evidenced by premature deliveries or intrauterine deaths at about the twenty-eighth week. *If vascular damage is graded from undoubtedly absent to the* maximum (in patients r

for the entire period of

cent, was 33 per cent,

in those with calcified pelvic arteries, and 97 per cent in those with nephropathy

The importance of abnormal vasomotor responses observed in the bulbar conjunctiva is recognized The changes for normal pregnancy consist of arteriolar constriction or spasm in the late third trimester and during labor When toxemia intervenes, these changes occur earlier. Arteriolar

etes; the first is char-

rteriolar constriction

This latter pattern is found in long-term diabetes or in ketoacidosis.

In pregnant diabetics the pattern normal for pregnancy appears early and is exaggerated. The two abnormal patterns of diabetes are exaggerated. Intravascular sludging, edema, exudate, hypoxia and starvation are inferred The changes seen in the conjunctiva are duplicated elsewhere, in the retina, kidney, uterus, placenta and fetus

D PLACENTAL FACTORS INFLUENCING COURSE OF PREGNANCY

The chemical abnormality which has concerned us for twenty years has been the imbalance of female sex hormones This imbalance is characterized by an abnormal rise of chorionic gonadotropin between the twenty-

[1] Snyder and Hoskins Anat Rec, *55*, 23, 1932
[2] Britton. Am Jour Physiol, *95*, 178, 1930
[2a] Parsmore and Schlossmann Jour Physiol, *92*, 459, 1938

fourth and thirty-sixth week of pregnancy, low levels of serum estrogen and low levels for pregnandiol The normal relation in pegnancy has been interpreted by Smith and Smith.[3,4] According to them the inter-

(alpha) has two modes for its breakdown, through the metabolic cycle and through oxidation In the metabolic cycle, estradiol is converted to estrone and estrone to estriol. In the oxidative breakdown of estradiol and estrone, inactive oxidation products are formed These oxidative breakdown products further stimulate the syncytial production of estrogen and progesterone

Early in pregnancy the oxidative breakdown is the important one Increasing quantities of estrogen and progesterone are produced More

estrogen levels fall The further complex interrelation of the placental and hypophyseal hormones has been postulated by George Van Smith as follows:

One of the functions of estrogen is to increase the vascularity in the pelvic organs and thereby the blood supply to the placenta Estrogen failure decreases the blood supply to the placenta Withdrawal of hormonal support then leads to decreased vascularity of the placenta and eventually labor is initiated This entire process in the normal individual is dependent upon pelvic vascular sufficiency It is possible that the normal process in the diabetic fails because of her pelvic vascular insufficiency

Premature withdrawal of sex hormonal support leads to toxemia, intrauterine death and preeclampsia The factual evidence that vascular insufficiency favors sex hormonal imbalance in diabetes is as follows: none of our patients with vascular disease had normal levels for sex hormones, and the more advanced the vascular damage, the more profound was the imbalance

Ninety-five per cent of our diabetics have a demonstrable imbalance defined as the rise of chorionic gonadotropin above 200 rat units per 100 cc of serum between weeks 24 and 36, or all of pregnandiol glucuronidate

[3] Smith and Smith W Jour Surg, *55*, 288, 1947.
[4] Williams, R H P 349, Loc cit, p 619

below the minimal level of the curve of Venning and Browne.[5] Among 47 cases with spontaneous normal hormonal balance the course and outcome was normal, 95 per cent viable salvage, no toxemia, no spontaneous premature deliveries. Among 113 with abnormal balance not treated, the viable salvage was 49 per cent, toxemia 33, spontaneous premature delivery 33 per cent.

To retest the correlation between the abnormal female sex hormone pattern and the course of obstetrical diabetes, patients were divided into four groups: (*a*) normal course, liveborn surviving infant, (*b*) toxemias, (*c*) spontaneous premature deliveries prior to the 35th week, and (*d*) nonsurviving infants. *The median curve was compared with the curve of Venning and the results are shown in Figures 37 to 41.*

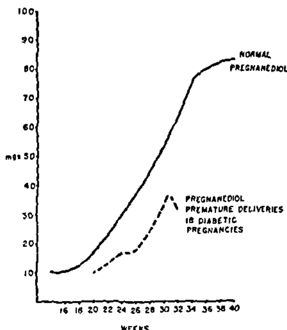


FIG 37 Spontaneous premature delivery Eighteen pregnancies terminating before the thirty-fourth week (White, Gillespie and Sexton, courtesy of Am Jour Obst and Gynec, *71*, 57, 1956)

Other chemical abnormalities have been observed by Hughes[6] and by Curtis[7] respectively, an increase in alkaline phoshatase and in deposition of glycogen The imbalance of female sex hormones, the high levels for alkaline and acid phosphatase suggest aging, premature aging of the placenta

The structure of the placenta of the diabetic deviates grossly from the normal in two respects, either by its abnormally large size or, the opposite,

[5] Venning and Browne Jour Biol Chem, *119*, 473, 1937
[6] Hughes Personal communication
[7] Curtis Personal Communication

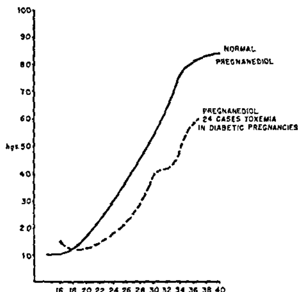


Fig 38 —Twenty-four cases complicated by toxemia (White, Gillespie and Sexton, Am Jour Obst and Gynec, 71, 57, 1956)

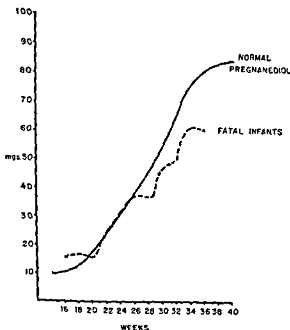


Fig 39 —Infants lost Forty-four cases (White, Gillespie and Sexton, Am Jour. Obst. and Gynec, 71, 57, 1956)

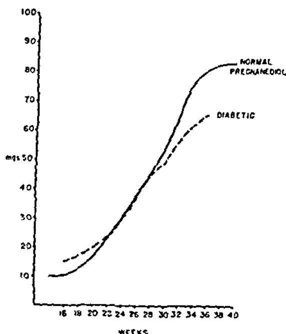


FIG 40 — Liveborn and surviving infants in pregnancies uncomplicated by premature delivery (before the thirty-fourth week) or by toxemia (173 cases). (White, Gillespie and Sexton, Am Jour. Obst. and Gynec , *71*, 57, 1956)

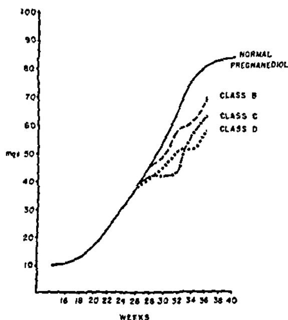


FIG 41 — Pregnanediol excretion in diabetic pregnancies by class compared with the normal. (White, Gillespie and Sexton, Am Jour. Obstet and Gynec., *71*, 57, 1956)

abnormally small size The large placenta has an abnormally large cord, which pulsates longer than expected, and is, in its vascular pattern, characteristically more mature and more senile than the gestational age

E. THE PLACENTA OF THE DIABETIC MOTHER

Previous studies of the placentas of diabetic women have not shown a definite and consistent pathologic change from either the gross or microscopic standpoint Reis, De Costa and Allweiss[8] examined the placentas from 10 diabetic women who had received no hormonal treatment and [illegible]

[illegible]

maturely Admittedly this would be undesirable in the diabetic whose tendency is to show rapid maturity. A study of our material by Dr. Donald G MacKay of Boston Lying-In Hospital showed changes characteristic of immaturity rather than those of maturity.

[illegible]

The cytotrophoblastic cells of the Langhans layer were quite prominent in these edematous villi and many were undergoing mitotic division The syncytium and decidua did not reveal any pathologic change.

Burstein, Soule and Blumenthal[10] studied the placentas of twenty diabetic patients, comparing them with fifty normal term placentas and fifty-six specimens from cases of toxemia and hypertension. Essentially the umbilical vessels showed no deviation from the non-diabetic. Placental

[8] Reis, De Costa and Allweiss Am. Jour Obst and Gynec, *60*, 1023, 1950
[9] Somers, Lawley and Hertig Ibid, *58*, 1010, 1949
[10] Burnstein, Soule and Blumenthal Ibid, *74*, 96, 1957

tion was more intense in the chorionic plate than in normal pregnancy and was comparable to the toxemic hypertensive group. The villi showed changes seen in hypertensive toxemic cases consisting of calcification of the basement membrane. Syncytial buds and stroma of villi showed arborization of PAS positive fibrils forming networks of this material and were more marked than in the normal and hypertensive toxemic groups. A positive correlation between these changes and fetal loss was found

The small placenta is seen more often in diabetics with hypertension or nephropathy. Infarcts and occlusive vascular disease occur.

The gross functional placental change consists of the abnormal overproduction of amniotic fluid. If diuretic measures are not employed, the quantity reaches some ten times the normal of 750 cc., producing undesirable pressure upon cord and fetus and often rupturing membranes in the previable period Not visible but inferred are the abnormal vasomotor responses seen at the microscopic level in the bulbar conjunctiva.

F FETAL FACTORS INFLUENCING COURSE OF PREGNANCY

The fetus, too, has chemical, structural and functional abnormalities The chemical abnormalities which have concerned us for a long time include hypoglycemia, the low pH and high pCO_2 Hypoglycemia is now for the most part considered physiological

Hypoglycemia.—In support of the theory of the harmful influence

the even lower range in the premature infant. An infant normal at term shows blood-sugar levels in the range of 25 to 60 mgs. The range of the premature infant is 17 to 40 mgs

The minimum, average and maximum blood sugars for the first day of life for the normal infants of normal mothers were found by Lucas *et al* [11] to be 40, 50 and 60 mgs. per cent respectively Kitteringham and Austin[12] found the level of blood sugar of the newborn normal infant to be 55 to 75 mgs McKittrick[13] demonstrated the same behavior and reports a normal infant whose blood sugar fell to 28 mgs. but who remained asymptomatic *Comparative blood sugar studies in the parturient woman and*

[10a]Platou Lancet, ... Brit Med Jour 1 360 1915
Woodrow Brit Med
Assn, 107, 919, 1936 I
1920 Wiener Am Jo
Path and Lab Med,
Nevinny and Schretter
Nevinny Ztschr f G
Gynak, 64, 817, 1930 I
Med. Soc, 134, 167, 19
[11] Lucas, Dearing, H
[12] Kitteringham and
[13] McKittrick Personal Communication

the newborn were made by Hanley and Horn.[14] The average maternal macro blood sugar was 106 and micro 128 7 and 126 8. Umbilical venous blood at birth was macro 111.3 and micro 111.7 mgs Umbilical arterial blood was macro 88 3 mgs, micro 95.4 and 96 4 mgs. One hour after delivery heel or finger blood was 80.3. Six hours after delivery fontanelle was macro 66 0, heel was 77.1 and finger 77 5 mgs

The average blood sugar for 38 of our cases at birth was 100 mgs In four hours i

(26 cases).

in four hour

9 mgs., was

twitching

Barns[15] likewise discountenances hypoglycemia in the infants of diabetic mothers and the experimental data of Himwich, Fazekas and Homburger[16] indicate that low blood-sugar levels were well tolerated in infancy. Infant rats survive hypoglycemia longer than do adults because of their lower cerebral metabolic requirements

curves, identical, may be superimposed one upon another

Hyperglycemia of the infant may occur coincidentally with maternal hypoglycemia Blood sugar levels below 20 mgs may be considered

prior to the normal

G FETAL ABNORMALITIES

A birth weight exceeding the expected normal for the period of gestation occurs in 80 per cent of the infants of diabetic mothers.[17] The body length also exceeds the average for the chronological age. The body weight of the infant is influenced by three factors (*a*) fat, (*b*) edema, (*c*) large size of the organs The gross appearance and the depth of the adipose tissues measured at autopsy were evidence of the nutritional obesity

Edema occurred commonly in the infants It is evidenced by pitting, diuresis, total weight loss and obliteration of wrinkling The maximum weight loss in our infants was 2 pounds in three days and a near maximum of 1 pound in twelve hours The weight loss in seventy-two hours of 60 of the infants for whom data were available was on the average 10 5 ounces as compared with 6 3 ounces for 60 infants of non-diabetic mothers

[14] Hanley and Horn Am Jour Obst and Gynec, *46*, 502, 1943
[15] Barns Jour Obst and Gynec Brit Empire, *48*, 707, 1941
[16] Himwich, Fazekas and Homburger Endocrinol, *33*, 96, 1943
[17] Reed Proc Fourth Am. Cong Obst and Gynec, Am Jour Obst and Gynec, 61 4 Supp, 1951
[18] Fischer Zentralb f Gynek, *50*, 241, 1935

delivered during the same interval at the Faulkner Hospital. The range of weight loss was 0.5 to 32 ounces for infants of diabetics and 1 to 12 ounces for infants of non-diabetics.

Mild jaundice with normal blood counts and no tendency to bleed occurred in many of the infants of diabetic mothers prior to 1950. Prematurity appeared to be the most probable explanation. However, with the decrease in morbidity of these infants which has followed the present management (described on page 712) these infants have not been icteric

A description of the *visceromegaly* confirmed at autopsy of 50 infants appears under "Pathological Characteristics of the Infants of Diabetic Mothers."

II. PATHOLOGICAL CHARACTERISTICS OF THE INFANTS OF DIABETIC MOTHERS

The following is Dr. P M. LeCompte's[19] summary of his findings in a study of 50 autopsies on infants of our diabetic mothers performed at Faulkner Hospital from 1937 to 1949, inclusive.

"1. *Macrosomia.*—It is a clear-cut and widely recognized fact that the babies of diabetic mothers tend to be larger than normal. The tendency for

[illegible]

regard. The common tendency to use size alone as a criterion of maturity[20] is certainly open to question

"The hypothesis that the large size of the infant is due to overactivity of the maternal pituitary, a particularly attractive theory in relation to the 'prediabetic state,' is not as yet supported by adequate evidence.

"2 *Visceromegaly* —Enlargement of the heart is seen frequently enough to be significant Although it is probable that these hearts contain more glycogen than normal ones, the increased size can hardly be due to the glycogen deposit, unless one assumes that glycogen may make up more than 10 per cent of the weight of the heart Enlargement of the spleen and liver is seen in only a fraction of cases, and is not clearly significant. It may be due in part to relatively large amounts of hematopoietic tissue, although it is not clear that the latter is actually increased out of proportion to the age of the fetus.

"3. *Pancreas* —Two changes are found often enough to be considered significant: (*a*) hyperplasia of the islets of Langerhans and (*b*) infiltration of eosinophilic leukocytes The causes of both of these phenomena are obscure

"4. *Hematopoiesis* Extramedullary hematopoiesis (chiefly erythropoiesis), especially in the liver and spleen, has been cited as characteristic of these infants The significance of this finding is questionable when one

[19] Warren and LeCompte Loc cit, p 170
[20] Casagrande Am Jour Obst and Gynec, 37, 1028, 1939

considers the gestational age of the fetus If it is truly increased, the cause is not clear.

"5 *'Glycogen Nephrosis.'*—Deposition of glycogen in the renal tubules

percentage of cases, and may conceivably be due to a high concentration

y to an excess of insulin from the

of the placentas seemed to be definitely heavier than normal. Whether this is related to immaturity remains to be seen. No changes considered to be significant were found in the adrenal glands or other organs "

The most constant single finding in our infants was pulmonary hyaline

in relation to the abnormal vasomotor responses in pulmonary vessels

All the preceding abnormalities, maternal, placental and fetal, are not separate entities. Almost no patient with vascular damage had normal patterns for female sex hormones, and beta-lipoprotein levels, vascular changes in structure and response and imbalance of female sex hormones paralleled one another.

1 In the first method, non-intervention, the diabetic woman receives good treatment for diabetes and her obstetrical management is that of the normal woman This constitutes a denial that the diabetic woman, her placenta and infant, functionally, structurally or chemically differ from the normal in any way. The fetal loss with this management is 45 per cent, as best shown in the "Q" series reported in the British Empire

the viable fetal loss is 30 per cent

3 Dissatisfied with these results, the use of female sex hormones was added to our management in 1938 The *rationale includes the frequency* of the imbalance and its correctibility, the value of female sex hormones as lipid clearers, vaso dilators and as promotors of the normal growth of

J. CLASSIFICATION OF PREGNANT DIABETICS

Controversy exists because of the differences in types of diabetics There are many types of diabetics, clinical and subclinical, juvenile (total and adult) diabetics with and without vascular disease. End results vary [illegible]

[illegible] many obstetrical problems To clarify these differences, a classification has been attempted

The classification which we have found helpful is based upon the age at onset, the duration of diabetes and the presence or absence of vascular lesions. *It presupposes that diabetes with onset in childhood is of a more* malignant type than that which occurs in adult life; that measured in insulin production this group of patients represents total diabetes and [illegible]

[illegible] but that after 20 years, only one young patient in 10, and after 25 years, only one in 50 can be found completely free from at least minimal evidence of vascular damage; and, finally, that vascular damage in the diabetic carries with it the same hazards as vascular damage in the pregnancies of comparable women in the general population. The designation of the classification we employ is alphabetical, classes A through F.

Class A consists of subclinical diabetics, those patients in whom the diagnosis of diabetes is made upon the basis of a glucose tolerance test which differs little from normal It is not the practice of diabetic clinics to administer a glucose tolerance test if the diagnosis can be established on random blood sugars, so that these patients may have only minimal disturbance In the majority of our patients, the glucose tolerance test [illegible]

[illegible] demonstrated but may exist in a latent state Class D includes those [illegible]

[illegible] vascular lesions of the earliest varieties, namely, *the retinopathies* or calcification of the vessels of the legs Probably under the same heading should be our Class E, which has been separated because it was the first to attract our attention to the importance of vascular damage in pregnancy Namely, those patients where the vascular damage has progressed so far that the vessels of the pelvis can be demonstrated to contain calcium by *x*-ray Although this suggests medial sclerosis, characteristic of diabetes is intimal sclerosis in vessels ordinarily involved with the medial type of

lesions. Although the iliacs are the vessels usually shown, we believe that the ovarian and uterine arteries are similarly involved, and in the autopsied cases this concept has been confirmed. Class F, a dreaded group by any standard, includes those patients with albuminuria not accounted for by

rates. If we study the entire period of pregnancy where one expects a fetal salvage of some 87 per cent, we have found the following: in Class A, 100 per cent, Class B, 67 per cent; Class C, 48 per cent; Class D, 32 per cent; Class E, 13 per cent; and Class F, 3 per cent. These results were found in a group of 278 cases where the management consisted of good chemical control of diabetes and the best available obstetrical management but no female sex hormones. Much of the controversy in the obstetrical diabetic literature today concerns differences in types of patients treated and reported. Thus, today our most common class is D, and 70 per cent of our patients are in classes C through F.

A few general statements may be made about these classes. Class A can be managed with dietary regulation but otherwise as a woman without diabetes, although we consider Class B a mild group, it has proved a plaguing one for the obstetricians. These patients may have many insulin-producing cells and suffer much more from the diabetogenic action of pregnancy than do women whose diabetes is actually more severe at the start of pregnancy, women who have few or no insulin-producing cells. In a short period of time these milder diabetic patients develop a severe type

active and tend to produce the largest infants. Again they plague the obstetrician when pelvic delivery is attempted, for this is the type of patient where the head is extracted without difficulty but the short neck and the wide shoulders frequently cause obstetrical difficulties. Classes D, E and F prove to be treacherous from the point of view of intrauterine deaths in the 36th week. Infants born to these women tend to be small and, in spite of the duration of diabetes, they are more favorable candidates for pelvic delivery than are those of short duration. Because these patients have had experience in the management of the most malignant type of diabetes, they know how to manage the severe problems and the difficult problems which arise in pregnancy better than those women who under ordinary circumstances have a milder form of the disorder. This classification has, therefore, helped us in the individualizing of both medical and obstetrical management.

Studies Required for Evaluation.—To make this evaluation, in addition to the usual physical examination, patients require *x*-ray examinations of the legs to determine the presence or absence of calcification in the vessels. Ordinary bone technique is employed. Both legs should be *x*-rayed. Evaluation of the vessels of the pelvis and abdomen are not done during pregnancy.

J. CLASSIFICATION OF PREGNANT DIABETICS

Controversy exists because of the differences in types of diabetics. There are many types of diabetics, clinical and subclinical, juvenile (total and adult) diabetics with and without vascular disease. End results vary ... t easily remains ... in achieving a ... lisease presents many obstetrical problems. To clarify these differences, a classification has been attempted.

The classification which we have found helpful is based upon the age at onset, the duration of diabetes and the presence or absence of vascular lesions. It presupposes that diabetes with onset in childhood is of a more malignant type than that which occurs in adult life; that measured in insulin production this group of patients represents total diabetes and ...

but that after 20 years, only one young patient in 10, and after 25 years, only one in 50 can be found completely free from at least minimal evidence of vascular damage; and, finally, that vascular damage in the diabetic carries with it the same hazards as vascular damage in the pregnancies of comparable women in the general population. The designation of the classification we employ is alphabetical, classes A through F.

Class A consists of subclinical diabetics, those patients in whom the diagnosis of diabetes is made upon the basis of a glucose tolerance test which differs little from normal. It is not the practice of diabetic clinics to administer a glucose tolerance test if the diagnosis can be established on random blood sugars, so that these patients may have only minimal disturbance In the majority of our patients, the glucose tolerance test has actually been done in the non-pregnant state These patients under ordinary circumstances do not require insulin and very little dietary regulation Class B includes patients where the onset of diabetes has occurred ...t, under 10 years, that vascular ... Class C includes the patients ... 19 years, or where the duration ... where vascular damage is not demonstrated but may exist in a latent state Class D includes those patients whose diabetes is of more than 20 years' duration, where the absence of vascular damage is unlikely, or whose onset occurred under the age of 10, or patients who, regardless of age at onset or duration have developed vascular lesions of the earliest varieties, namely, the retinopathies or calcification of the vessels of the legs Probably under the same heading should be our Class E, which has been separated because it was the first to attract our attention to the importance of vascular damage in pregnancy Namely, those patients where the vascular damage has progressed so far that the vessels of the pelvis can be ... x-ray. Although this suggests medial ... intimal sclerosis in vessels ordinarily ...

tion of various hormones, particularly growth hormone, to the mothers during pregnancy. Large fetuses were also obtained, but to a lesser extent, when chorionic gonadotropin or thyrotropic hormone were given.

From our case histories the incidence of toxemia, abortion, intrauterine and perinatal deaths for the ten years prior to and ten years following diabetes onset are high and comparable. In the ten years prior to diabetes, toxemia was 10 per cent, abortion 42 per cent and perinatal loss 30 per cent

K. ZONDEK TESTS

False positive and negative tests occur in diabetes. The negative tests in our experience have been mostly due to submission of samples too early in pregnancy The false positives are possibly confused with the high titers for FSH seen at onset of diabetes and in diabetic amenorrhea.

L. COURSE OF DIABETES DURING PREGNANCY

The natural course of diabetes is markedly altered by pregnancy The effect may be temporary or permanent In the first trimester sensitivity to insulin is marked and the therapeutic dose may fall far below the pre-pregnancy level Many factors contribute, such as pituitary suppression, poor appetite, failure of absorption of food. By the second trimester the sensitivity to insulin becomes less As the quantity of diabetogenic hormonal production increases, insulin requirement increases and by the third trimester the dose may be two or three times the normal

alt

is

is

trimester Sheehan's syndrome is suspected if great sensitivity is observed after delivery

M OBJECTIVES IN MANAGEMENT

mothers

Management.—(*a*) DIET.—The methods used to obtain these objectives follow Physiological control of diabetes is sought by a caloric prescription

[20] Dolger and Herzstein Jour Am Med Assn, *125*, 931, 1944
[21] Hultquist and Engfeldt Acta endocrinol, *3*, 365, 1949
[22] Hoet Loc cit, p 59

The early evaluation of the retina is preferably made by an ophthalmologist who then has an excellent opportunity to observe slight but significant changes. If albuminuria exists and the nonprotein nitrogen, sediment, phenolsulfonephthalein tests are normal, urea clearance gives added information of the maternal and fetal hazards.

Fertility in Diabetes.—Prior to insulin therapy few diabetic women conceived. Bouchardat,[21] the great French clinician, saw no cases of pregnant diabetics and Naunyn,[22] in his wide experience, saw only one. They wrote as follows: "Dans le nombre si considerable de diabétiques qui sont venus me consulter, je n'ai pas mémoire d'avoir vu une seule femme enceinte," and "Ich kenne aus eigener Erfahrung nur einer Fall, der hieher gehört"

Statistics from obstetrical hospitals imply that diabetic women are not [illegible]

the exception rather than the rule.

Control of diabetes, however, may be an important factor in fertility and lack of control of diabetes may favor sterility. Thus Zondek[24] has shown that 18 per cent of all sterility cases can be explained on the basis of glycopenia uteri Increase in the fertility rate of diabetes has followed the use of insulin in 1922 and a greater increase in the number of diabetic pregnancies followed the use of slowly acting insulins which control the disease for longer periods of time.

[illegible]

for fertility is shown by the fact that individuals developing diabetes after age 18 had the lowest menarchial inception of any reported group of individuals

This high fertility potential rate accounts for the extraordinary penetrance of the disease

Prediabetic influences include the large size of a newborn infant, which in our prediabetic women exceeded 10 pounds in 15 per cent, in contrast to 3 per cent in the general population

[illegible] large infants

[21] Bouchardat Loc cit, p 19
[22] Naunyn Loc cit, p 55
[23] Barnes Loc cit, p 99
[24] Zondek Genital Functions and Their Hormonal Regulation, Baltimore, Williams and Wilkins, p 224, 1941
[25] Rix Med Klin, 29, 250, 1933
[illegible] 90, 502, 1928

TABLE 133.—CLASSIFICATION OF OBSTETRICAL CASES AND BASIC PLAN OF HORMONAL TREATMENT*

Class	A	B	C	D	E	F
Definition	*Glucose Tolerance Tests Diabetics*	*Onset DM over age 20 Duration DM 0–9 yrs Vascular disease—0*	*Onset DM age 10–19 Duration DM 10–19 yrs Vascular disease—0*	*Onset DM under age 10 Duration DM 20+ yrs Calcification legs, retinitis*	*Pts with calcified pelvic arteries*	*Pts with nephritis*
Hormone Dosage of { Delalutin 125 mg/cc, Delestrogen 10 mg/cc } weekly intramuscular injections						
Week of Pregnancy		*cc of each*	*cc of each*	*cc of each*	*cc of each*	*cc of each*
0–16		1	1	2.5	2.5	2.5
17–19		1	1	5	5	5
20–23		2.5	2.5	7.5	7.5	7.5
24–29		5	5	10	10	10
30–33		7.5	7.5	12	12	12
34–		10	10	12.5–15	12.5–15	12.5–15
Hormone Dosage of Progesterone and Stilbestrol 50 mg/cc daily injections						
Week of Pregnancy		*mg of each*	*mg of each*	*mg of each*	*mg of each*	*mg of each*
0–16		25	25	25	25	25
17–19		25	25	50	50	50
20–23		50	50	100	100	100
24–29		100	100	125	125	125
30–33		100	100	150	150	150
34–		125	125	200	200–250	200–250

Therapy regulation based upon 1. Weekly serum chorionic gonadotropin and urinary pregnandiol (glucoronidate) levels, and
2. Clinical evidence of disturbed water balance

* *Delalutin and Delestrogen supplied by* the E. R. Squibb and Sons, Co. Proluton supplied by the Schering Corp.

of 30 calories per kilogram of ideal body weight for height and age. The increase during pregnancy for the optimal 15-pound gain is about 200

desirable, more than 1.5 grams is a hardship for the patient. The remainder of the calories is given in fat.

(*b*) INSULIN.—The insulin prescription to achieve physiological control is often difficult. Intermediate-acting insulins must be given usually in split schedule before breakfast and at bedtime by the beginning of the third trimester, sometimes supplemented with additional doses of regular insulin in the pre-lunch and pre-supper periods. The degree of control sought is *normal glycemia before meals and glycosuria below 10 per cent* of the carbohydrate intake. Intensification of diabetes is complicated by the low renal threshold for glucose and for acetone.

(*c*) DIURETICS may be given as indicated Our practice is routine administration of ammonium chloride in 4-gram daily doses, sometimes alternating with diamox Currently the value of Diuril is being explored. By the twenty-eighth week the majority receive mercuhydrin weekly, by the thirty-fourth week biweekly. Diuretics are omitted 48 hours prior to *planned deliveries.*

When medical measures fail to prevent hydramnios, trans-abdominal amniotomy is done, by choice not earlier than two weeks prior to the expected date of good viability This has been done 16 times, repeated in 3 patients without precipitating labor.

Sodium is restricted moderately to 1 gram daily except when Diuril is used This sodium restriction imposes a hardship, since the diabetic's usual consumption of sodium chloride is as high as 20 grams daily.

(*d*) USE OF FEMALE SEX HORMONES —*The controversial part of our plan for therapy is the use of female sex hormones* At the present time our first choice is the long-acting variety (Delalutin and Delestrogen). These may be administered no more often than once weekly. Formerly, our patients received daily intramuscular injections of stilbestrol and

at the first visit and is shown in Table 135

The indications for increase in therapy include failure of the chorionic

upon median values for excretion of pregnanediol, support the thesis that the imbalance of female sex hormone characterizes abnormal pregnancy and poor outcome The most abnormal curve was found in those patients where the delivery occurred spontaneously prior to week 34 (See Fig 37) An almost equally abnormal curve was found in those patients who had

our "response" cases and the second our "no response" cases In our series, 60 per cent of treated cases fell into the "response" classification while the remainder were considered as having "no response." These patients had been treated over a period of thirteen years during which time duration and quantity of treatment had been increased By present standards earlier treatment was inadequate.

TABLE 136—PREMATURE DELIVERY BY HORMONAL LEVEL AND TREATMENT

Hormonal Level	Total Cases	Premature Delivery No	Premature Delivery Per cent
Normal Untreated	47	0	0
Abnormal Untreated	98	33	33
Abnormal Treated	380	65	17

The entire series of patients was divided then into three groups according to whether or not they received therapy and, if so, whether or not laboratory findings indicated that therapy was affecting the existing hormone levels When this division was made between groups of cases and the incidence of abnormal obstetrical problems within groups compared, the results were striking

We included patients who, during the third trimester of pregnancy, developed one or more of the following conditions: intrauterine death of the fetus, marked polyhydramnios with associated edema or albuminuria, preeclampsia and premature onset of labor

TABLE 137—CORRELATION OF LABORATORY RESPONSE TO HORMONAL THERAPY AND ABNORMAL OBSTETRICAL COURSE

Class	Abnormal Untreated Per cent	Abnormal Treated with (a) No Response Per cent	Abnormal Treated with (b) Response Per cent
A		Not Treated	
B	66	45	33
C	68	70	28
D	75	73	43
E	Insuff Cases	85	43
F		Insufficient Cases	

The results of [illegible]
in [illegible]
ma [illegible]
group than in the "no response" or untreated groups In fact, the difference between the latter two groups is very slight. Thus, in class B, 66 per cent of the untreated cases had abnormal obstetrical courses on the basis [illegible] esponse" groups showed [illegible] ectively. In the more [illegible] Classes C and D aver-

suggestion that the progression of vascular damage favors the hormonal

appear to indicate that when therapy is administered but the imbalance is not corrected the obstetric course is as abnormal as when no therapy is given. The fetal mortality also remains high when therapy is given and the imbalance not corrected, but falls when the imbalance is corrected.

Response and No Response Groups—Course and Outcome.—The success of hormonal therapy depends upon chemical response. To re-evaluate

showed positive correlation between abnormal levels of one or other sex hormones and the development of clinically demonstrable obstetrical abnormalities.

TABLE 134.—LATE SURVIVAL BY HORMONAL LEVEL AND TREATMENT

Hormonal Level	*Total Cases*	*Live Births* *No*	*Per cent*
Normal Untreated	47	45	96
Abnormal Untreated	98	51	52
Abnormal Treated	380	345	90

TABLE 135.—INCIDENCE OF TOXEMIA ACCORDING TO HORMONAL BALANCE AND THERAPY

Hormonal Level	*Total Cases*	*Cases Developing Toxemia* *No*	*Per cent*
Normal	47	0	0
Abnormal Untreated plus Abnormal Treated in the Third Trimester	116	38	33
Abnormal Treated in the First Trimester	362	26	7

The records of the patients were divided into two groups: those with abnormal hormone levels who received no therapy and those in whom an attempt had been made to correct the abnormal endocrine balance by replacement treatment. When this initial division had been completed it was evident that a second subdivision was necessary in the treated group. This second grouping was based upon laboratory evidence of response to therapy. It was apparent that treated cases fell into two categories, the first of which showed normal levels of hormone assay during therapy and

Complications of Hormone Treatment.—No side reactions have occurred. *Tests for liver function done at weekly intervals have remained* completely normal. Injection abscesses plague us somewhat. Too frequently the hormones are administered subcutaneously rather than intramuscularly, *or a sterile abscess develops from a hematoma.* *Hormones in* aqueous bases have proved more hazardous to our patients than those in oil solvents. No abscesses have developed in 100 cases treated with Delalutin

long-acting stilbestrol developed hyperplastic endometritis requiring dilatation and curettage on one or more occasions and, in some instances, repeated blood transfusions.

Experience of Others Making Determinations for Sex Hormones in Diabetic Pregnancies and Their Results With Sex Endocrine Therapy.—Two series of patients have been observed, studied and treated in a manner comparable to ours and yet with certain distinct differences. The first series consisting of 21 patients was studied, treated and reported by Crampton, Palmer, Steenrod and Davis.[35] They report a 66.6 per cent survival in patients treated with *oral* stilbestrol and intramuscular progesterone,

stilbestrol and intramuscular progesterone the fetal survival was 66.7 per

ionic gonadotropin.

Loraine found chorionic gonadotropin elevated in 6 out of 14 diabetics. Those treated with *oral* stilbestrol showed an escape phenomenon.

[33] Venning and Browne. Loc. cit., p. 691.
[34] Astwood and Jones. Jour. Biol. Chem., *137*, 397, 1941.
[35] Crampton, Palmer, Steenrod and Davis. Proc. Amer. Diabetes Assoc., *10*, 93, 1950.
[36] Keitz, Keaty and Hellbourn. South. Med. Jour., *43*, 803, 1950.

aged 70 per cent abnormal obstetrical courses in both untreated and "no response" groups, while the "response" cases averaged 28 per cent to 43 per cent respectively

In class E, "no response," abnormalities were 85 per cent as compared with a "response" incidence of 43 per cent. Class F cases were too few in number to warrant drawing conclusions from this source.

The correlation of laboratory response to hormonal therapy and fetal loss was also striking. In class B, the fetal mortality in untreated cases was 20 per cent, 7 per cent in the "no response" group, 13 per cent in the "response" group In classes C and D the fetal mortality in untreated cases was 25 and 46 per cent respectively, and 13 and 17 per cent in "no response" cases, with 1 and 7 per cent in "response" cases, (Table 138).

TABLE 138 —CORRELATION OF LABORATORY RESPONSE TO HORMONAL THERAPY AND FETAL LOSS

Class	*Abnormal Untreated Per cent*	*Abnormal Treated with* (a) *No Response Per cent*	(b) *Response Per cent*
A		Not Treated	
B	20	7	13
C	25	13	1
D	46	17	7
E	Insufficient Cases	62	29
F		Insufficient Cases	

In class E there were too few untreated cases to be significant. The fetal loss was 62 per cent in the "no response" group and 29 per cent in the "response" group

In our whole series of cases it was possible to prognosticate from the laboratory studies whether or not a normal or abnormal course was to be expected in 80 per cent of the cases.

Regulation of Hormonal Therapy.—The dose is regulated by weekly determinations for serum chorionic gonadotropin and by urinary pregnandiol excretion. If either is abnormal the patient is advanced to the next four-week period of therapy Clinical evidence of hydramnios or preeclampsia are additional indications for increasing the dosage of endocrine treatment

Bio-assay and Chemical Methods.—The serum to be tested for chorionic gonadotropin is precipitated with ethanol and stands overnight It is then extracted with ether and the residue suspended in 6 cc. of normal saline Since we are attempting to routinize procedures, low levels of gonadotropin are not determined The following amounts of sera are used 0 5, 0 3, 0 1 and 0 075 to give readings of 200, 333, 500, 666, 1000 and 1500 rat units per 100 cc of serum Twenty-one-day-old rats weighing 35 to 45 grams are injected tw[illegible]
the sixth day the rats are necropsied [illegible]

infants resemble individuals with Cushing's disease which does not appear to be an adequate explanation for their respiratory difficulty but may explain their tendency towards easy hemorrhage. Their excretion for 17-ketosteroids and 17-hydroxysteroids exceeds that of other infants Congestive heart failure has been suggested by the large heart, large liver and large spleen, so that such infants have been digitalized in many nurseries with the following dose: 0 03–0 05 mg per pound body weight, one-half stat, one-quarter at six hours and one-quarter at twelve hours.

The correction of the neonatal respiratory embarrassment in all infants continues to defy therapeutic programs The infant of the diabetic mother may show no abnormal signs and may have a completely normal course or may exhibit respiratory distress immediately after birth. Frequently the signs of respiratory distress may be present, but minimal at birth and become striking in their manifestations within a few hours following delivery The signs consist of increased respiratory rate, with or without cyanosis, together with retractions of the soft tissues of the chest wall and a constant complaining cry Examination reveals poor aeration of the lungs and inspiratory rales which are inconstant but heard throughout the lung fields X-ray reveals a fine granular type of infiltration The respiratory distress becomes increasingly severe over the next hours of life and the infant dies of respiratory failure after 25 to 72 hours, or gradually begins to improve and recovers completely over the same period Cases coming to autopsy show pulmonary hyaline membranes In our fatal cases they were present unless congenital anomalies or birth trauma accounted for death

During these early postnatal days, certain chemical changes occur Hypoglycemia, to which neonatal deaths were formerly attributed, is now known to be physiological for the first week of life Elevation of the hemoglobin and nucleated red cell counts are comparable in degree to these same findings in normal premature infants Blood oxygen levels may be low Disturbed acid base balance occurs Low levels of potassium and increased excretion of sodium and chloride have been observed in our patients and elsewhere

In a small series of cases increased levels of desoxycortisone and increased excretion of 17-ketosteroid and of 17-hydroxysteroids have been demonstrated Eosinophile counts were found to be comparable to those of other newborn infants

Congenital anomalies – These have often been reported and have occurred in 80 per cent of the infants of our diabetic mothers compared with the expected incidence of 1 8 per cent They account for 14 per cent of the fetal deaths and include defects of the skull and heart, cysts of the kidney, ovary, pancreas, mouth, angioma, syndactylism, claw hand, club foot, web toes, congenital hip, dwarfism, feeblemindedness, and Mongolian idiocy. Anomalies usually of mesenchymatous tissue have been noted in diabetics. Genetic origin appears to be the most logical explanation

O INFANCY AND EARLY CHILDHOOD

Congenital anomalies continue to exact their toll in the infancy period of between two weeks and twelve months. For the most part these are

The results of the British Medical Research Council investigation of pregnancy in diabetes confirm our experience only in part. They confirm the occurrence of the imbalance of female sex hormones, their precedence in relation to abnormal course and outcome, the ability to correct the imbalance with female sex hormonal therapy, but do not confirm better fetal survival with the use of female sex hormonal therapy. However, they used ethisterone and stilboestrol administered orally in a dose schedule irrespective of classification and response. The outcome showed 30 and 32 per cent fetal loss in treated and untreated cases selected to exclude retinopathy. Our comparable loss in the same period was 9 per cent.

Examination and Hospitalization.—*To facilitate management, the patients are examined weekly, jointly by the obstetrician and internist.* Hospitalization is advised two weeks prior to the expected delivery date.

Delivery.—The timing of delivery is of greatest importance. Class A patients, sub-clinical diabetics, are carried to term and we expect that the majority of these patients will be delivered pelvically By the method of trial and error, our Class B and C patients are carried if possible to the end of week 37. Those in Classes D, E and F, the vascular group, are re-evaluated at the end of week 35 If the infant appears small and the case uncomplicated, then an effort is made to carry the pregnancy longer. The choice for type of delivery is the obstetrician's. More patients are given a trial of labor Induction has usually been attempted with rupture of the membranes in favorable cases; in those which are not so favorable, priming with Pitocin and then when the cervix is statisfactory, rupture of membranes. An eight-hour trial of labor is given If the patient has not progressed satisfactorily in this time, Cesarean section is done. The short-term case [illegible] than is the long [illegible] short satisfactor [illegible] atient *receives no long-acting insulin for about 24 hours prior to the scheduled* time for delivery If labor is induced in the morning, we give half the usual dose of the long-acting insulin and then supplement it immediately after delivery.

N NEONATAL CARE

The care of the infant in the immediate postnatal period is of greatest importance. The following conditions have been named as responsible for poor behavior in these infants when it occurs. (1) hypoglycemia due to hyperinsulinism, (2) primary pneumonia, (3) congestive heart failure, (4) Cushing's syndrome, (5) respiratory acidosis, (6) hypoxia, (7) pulmonary hyaline membrane with atelectasis Some of these conditions [illegible]

[illegible] routinely. It is avoided because of the tendency of these infants toward edema. Primary pneumonia does not appear to be an important cause of poor behavior but may complicate the hyaline membrane syndrome These

amount in only 4 per cent. Among the daughters of diabetic mothers, 20 per cent, whereas among the daughters of diabetic fathers, 2 per cent showed this positive deviation. Sons of diabetic mothers showed greater positive deviations in height—more than 3 inches greater than the expected in 51 per cent, sons of diabetic fathers in 31 per cent. Birth weights were more often higher and bone age more often advanced in children of diabetic mothers

In the two characteristics which influence most, anomalies and diabetes, the incidence was nearly equal. The search for anomalies should be extended to include x-ray studies. Lethal anomalies were excluded by the nature of this comparative study

There is only one indication for interruption of pregnancy—advanced renal failure.

Results.—Maternal case survival was 99 7 per cent. The follow-up of patients delivered in 1937, showed that in 9 of the 10, the twenty-year survival was reached Toxemia incidence is 3 per cent. Previable losses are 10 per cent (prior to week 28)

Typical diabetic retinopathy or nephropathy may be revealed in pregnancy In 1950, Dr W. P Beetham called our attention to the fact that these lesions not only appeared but often persisted after delivery Revision of therapy was made at that time The only possible change was in female sex hormonal dose Subsequently existing retinopathies have not been progressive and new retinopathies have not been precipitated.

The total viable fetal salvage approaches 90 per cent (87) By class with therapy total fetal salvage is as follows A, 100 per cent, B, 92 per cent, C, 86 per cent, D, 85 per cent, E, 76 per cent and F, 59 per cent

TABLE 139.—900 VIABLE CASES TREATED WITH FEMALE SEX HORMONES

January 1938—June 1958

Class	No Cases	Class Per cent	Fetal Survival Per cent
A	15	2	100
B	226	25	92
C	283	32	86
D	275	30	85
E	58	6	76
F	43	5	59

Total Viable Fetal and Infant Survival—87 per cent

Adequate time has not elapsed to evaluate measures for the prevention of diabetes and bizarre growth patterns, but programs of diet regulation, insulin and oral substitute have been inaugurated

Summary—In our experience prediabetes, although influencing the immediate and remote course of infants born to these mothers, was less injurious than diabetes per se which if of short duration in turn was less serious than diabetes complicated with vascular degeneration.

Chemical control of diabetes diminishes the hazards of fetal death from hypoglycemia and ketoacidosis to which the intensification of diabetes from the placental production of diabetogenic hormones make diabetic women liable

cardiac. From the end of the first year up to age six the behavior of these children is not remarkable.

At age six the excessive rates of linear growth and excessive gains in weight become manifest. A series of 105 children of our diabetic mothers showed at the time of their examination, when they were from 13 months to 20 years of age, that gigantism was prevalent among sons, 57 per cent of whom were from 3 to 10 inches above the Englebach standard, and 50 per cent of them weighed more than 30 pounds above the standard weight for height and age.[37] Daughters showed the same plus deviations in 31 per cent for height and 20 per cent for weight. Twenty-one per cent of the boys rated greater than the 2 per cent auxodrome level on the Wetzel grid and fell in channels A_3 and A_4, as did 14 per cent of the girls Bone development, estimated by comparison with the Todd atlas, exceeded the chronological age by 12 months in 48 per cent of the cases. Congenital anomalies were found on physical examination in 17 per cent.

A second striking deviation from the normal was the evidence of diabetes. In the general population one child in 2500 develops diabetes In our population 9 per cent showed undoubted diabetes and 14 per cent showed borderline glucose tolerance curves with capillary blood sugar values between 200 and 250 mg. Another deviation from the normal was an apparently well-defined change of the vascular pattern of the smaller vessels in the conjunctiva examined at the microscopic level. This occurred in 75 per cent of the children classified as diabetic or borderline. A positive correlation was found between the degree of vascular change in the smaller blood vessels of the conjunctiva, the abnormal glucose tolerance tests and the high Wetzel grid rating[38]

Comparable data were collected on children of diabetic fathers The survival rate of their offspring is high, viable survival being that of the general population *Heavy birth weights of infants of prediabetic and diabetic fathers have been described*[39] Seven per cent of the infants of pre-diabetic fathers and 1 per cent of the infants of diabetic fathers in this series were more than ten pounds at birth

Using identical standards, the positive deviations for weight of more than 30 pounds were found only in 4 per cent of the sons and 2 per cent of the daughters of diabetic fathers The comparable deviations in height were 31 per cent for both boys and girls The bone growth was advanced in 35 per cent of the children of diabetic fathers Congenital anomalies were found on physical examination in 15 per cent Twenty-one per cent

whose sons exceeded the expected weight by 30 pounds in 50 per cent, whereas the sons of diabetic fathers exceeded the expected weight in this

[37] White, Duckers, Koshy, Med Clin North Am, 37, 1481, 1953
[38] Ditzel, White, and Duckers Loc cit, p 56
[39] Jackson Lancet, 2, 625, 1955

Chapter 29

NON-DIABETIC MELITURIA

Alexander Marble, M D.

A INCIDENCE

The finding of sugar in the urine must not be dismissed lightly, but pains should be taken to establish as soon as possible a definite diagnosis, that of

of such a condition is, therefore, the duty of the physician.

Some years ago a study[1] was made of 14,000 patients who had come for diagnosis or treatment of supposed diabetes in the thirty-eight years from 1897 to 1935 It was found that of these there were 2065 patients, or 14 8

of changed diagnosis, 1946 or 13 9 per cent of the total group remained in whom diabetes had not been proved This experience is of interest in that

attempt to ascertain this

In a health survey of nearly 150,000 young people employed or seeking

in urine Diabetes mellitus was noted in 0 1 per cent

The next large-scale study was that carried out by Blotner and Hyde[3] during World War II They found that of 45,650 consecutive selectees and

Med Sci, *197*, 533, 1939
S Government Printing Office,

Estrogen and progesterone appear to increase vascularity and decrease the fetal mortality related to vascular damage Female sex hormonal therapy appears to prevent the vascular characteristic of the diabetic placenta, stimulates the placental pituitary relations and replaces the hormonal deficit, lessening the chances for fetal loss due to the rapid maturity of the placenta.

Of the six possible explanations for the poor behavior and neonatal deaths in infants born to diabetic mothers (hypoglycemia, congestive heart failure, primary pneumonia, respiratory acidosis, hypokalemia and pulmonary hyaline membrane with atelectasis), pulmonary hyaline membrane appears to be the most significant. (Hypoglycemia is physiological, the pneumonia is secondary, congestive heart failure is not proved, and respiratory acidosis may be effect rather than cause.) Programs for prevention and treatment of pulmonary hyaline membranes based upon the concept tha' "

(

by

diabetic fathers. Overproduction of insulin by their hyperplastic islets may promote the excessive rate and quality of growth

fat

tolerance tests even before age twenty The data support the concept that the transmission proceeds through Mendelian recessive genes. Programs for identification of diabetes and protection during diabetogenic experiences must be organized

Female sex hormonal therapy added to chemical control of diabetes, measures to prevent or correct hydramnios, careful selection of time and

it survival to nearly 90 per cent,

per cent

rse and outcome but vascular changes are assuming greatest importance. In management, good chemical control is preventive, early timing of the delivery corrective, the use of female sex hormones protective

Better results will follow prevention of pre-pregnancy vascular disease, and the discovery of better vaso drugs during pregnancy

sumption is probably true also if the amount of urinary sugar found is large. The greatest aid in diagnosis is the level of the blood sugar The [illegible]

[illegible]

presents himself three or more hours after a meal and at such a time a [illegible]

[illegible]

taken of the food eaten and a second examination of blood and urine made If these tests are not conclusive, other examinations of blood and urine may be made subsequently, taking specimens as before, one hour after a liberal [illegible]

[illegible]

the urine, to determine the *type* of sugar being excreted.

In any uncertain instance one must fall back upon clinical data to sup- [illegible]

[illegible]

tient is worthy of comment in this connection Case 4534 came to us in 1925 with 3 per cent sugar in the urine and we found a blood sugar of 0 14 per cent fasting The child even went to a diabetic camp and took insulin nine years under the supervision of a whole group of doctors As years went by, however, it was noted that repeatedly blood-sugar tests were normal and we finally suspected and then proved that she had renal glycosuria Incidentally the insulin did no harm She was alive and well in 1958

C CLASSIFICATION OF GLYCOSURIAS

It is helpful to group under definite headings the various conditions in which sugar is found in the urine Our classification includes four types. (1) diabetes mellitus, (2) potential diabetes, (3) renal glycosuria and (4) [illegible]

[illegible]

factory diagnosis, but at times a most convenient one We formerly used it for those individuals with glycosuria closely related to diet, who easily become sugar-free with slight restrictions, and whose true blood sugar is below 110 mg per cent fasting and never reaches 150 mg per cent after a meal. The number of patients listed in this group was formerly fairly large,

volunteers, aged eighteen to forty-five years, examined at the Boston Induction Station, 367 or 0 8 per cent had glycosuria. Among the 367 the following diagnoses were made: 208 cases of diabetes mellitus, 126 of transient glycosuria and 33 of renal glycosuria. In a second study which included 69,088 selectees, aged eighteen to thirty-seven years, Blotner[4]

was more than twice as great in the second as in the first study.

Another study carried out on young adults was that of Watson,[5] who found the incidence of glycosuria in routine examinations of college stu-

As

tunity for learning the incidence of glycosuria in the general population. *In the St. Louis survey reported by MacBryde,[6] 17,451 examinations were* made; glycosuria was found in 3.5 per cent. In the Dayton Survey reported by Sharkey *et al*,[7] 4 3 per cent of 69,159 persons had glycosuria. In an over-all tabulation made by the Diabetes Detection Committee of the American Diabetes Association for the year 1949-50, it was found that 3 8 per cent of 198,443 persons had glycosuria[8]

The accumulated experience to date suggests that on random sampling the incidence of glycosuria in the general population is about 3 5-4 0 per

diabetic type

B DIAGNOSIS OF THE TYPE OF MELITURIA

When sugar has been found in the urine, these questions arise. Has this patient true diabetes mellitus? If not, what is the cause of the urinary sugar? What is the nature of the sugar and what steps should be taken to establish its identity? What treatment should be prescribed?

Naturally, if the patient presents the classical symptoms and signs of diabetes, or if in his case there is a family history of diabetes, it is likely that the presenting condition is one of true diabetes mellitus. This pre-

[4] Blotner Loc cit, p 48
[5] Watson Endocrinology, *25*, 845, 1939
[6] MacBryde Jour Missouri Med Assn, *41*, 776, 1949
[7] Sharkey, Troup, Miller, Van Kirk, Freeman and Williams Jour Am Med Assn, *144*, 914, 1950
[8] Report of Committee on Diabetes Detection, Proc Amer Diabetes Assn *10*, 262, 1950

[illegible]

ketosis develops during starvation rather than following dietary excesses, diabetic symptoms, including polyuria, are absent and the condition, without treatment, is not progressive. Renal glycosuria is asymptomatic except that some patients complain of easy fatigability and lassitude. Whether these symptoms are to be attributed to the disorder *per se* is difficult to decide.

As far as we have been able to discover, there is no published report of an autopsy in a case of renal glycosuria (with a threshold low enough to permit constant glycosuria even in the fasting state) uncomplicated by serious metabolic disease. The case of Grote and Heilman[14] was one of true diabetes mellitus associated with a very low renal threshold, the patient died of pneumonia following resection of the stomach for carcinoma.

Certain workers[15, 16] believe that renal glycosuria may progress to true diabetes. With one possible exception, no such case has been seen in this clinic. In the study of approximately 2000 patients included in the first [illegible]

[illegible]

values above normal but there was no progression over a period of forty-one years. In 1944 following a sugar tolerance test which, except for glycosuria, was unequivocably normal, she was accepted into the WAVES. She died Dec[illegible]

duration is C[illegible]

was first disc[illegible]

years sugar has been found in sizable amounts at every examination of the urine and at times in quantities as great as 5 per cent or more. Throughout

[9] Fowler. Ann Int Med, *7*, 518, 1933.
[10] Bland. Ibid, *29*, 461, 1948.
[11] Blotner and Hyde. Jour Am Med Assn, *122*, 432, 1943.
[12] Marble. Am Jour Med Sci, *183*, 811, 1932.
[13] Smith and Smith. Arch Int Med, *60*, 119, 1937.
[14] Grote and Heilman. Centralbl f allg Path u path Anat, *64*, 65, 1935.
[15] Vegter. Jahrb f Kinderh, *150*, 282, 1937–1938.
[16] Bertram. P. 25, loc cit, p 82.

but diminished in recent years not because similar cases are not now seen,
In
" in

TABLE 140.—CLASSIFICATION OF APPROXIMATELY 50,000 PATIENTS WITH MELITURIA.

Case No.	D.M.	P.D.	R.G.	Unc.	Pentosuria	Levulosuria	Deferred
0 to 5000	4311	124	23	509*	2	–	—
5001 to 10000	4217	80	20	637	3	1	11*
10001 to 15000	4316	8	9	538	1	1	97
15001 to 20000	4137	5	12	336	3	1	206
20001 to 25000	4278	—	7	321	–	1	390
25001 to 30000	4272	26	6	338	–	–	358
30001 to 35000	4272	67	2	209	1	–	449
35001 to 40000	4059	64	5	167	–	–	705
40001 to 45000	4111	5	6	189	–	–	688
45001 to 50000	4174	0	4	260	–	–	561
	42,537	379	94†	3509	10	4	3465

* One patient in this series numbered twice

† Includes 9 cases of renal glycosuria of pregnancy.

Those patients originally classified as potential diabetics, included in the first 14,000 cases (first seen between 1900 and 1935), were traced to May 1, 1937. The fact that by this time 16.7 per cent had developed diabetes emphasizes that one must be cautious and remember that time alone

be asked to eliminate
ve the blood and urine
examined every three months, for the first year, and at six-or twelve-month intervals thereafter. It is important that potential diabetics keep their body weight at, or slightly below, the average normal figure for age and height

Renal Glycosuria.—Renal glycosuria, incorrectly termed "renal dia-

from time to time in the

sugar In so doing, numerous cases are discarded (placed in the "unclassified glycosuria" group) which would be termed renal glycosuria by many workers However, to include all cases in which the renal threshold is

sense described This group includes 9 cases of renal g
nancy

a family group of 33 persons Among 22 of our own cases of renal glycosuria reported in 1932,[26] there were 15 in which a family history of diabetes was obtained.

It should be kept in mind that, as Lawrence[27] has pointed out, in certain cases of true diabetes mellitus a low renal threshold may exist. Such an individual is Case 8471, who must be content to show small quantities of urinary sugar in order to avoid insulin reactions, other patients include Cases 7317 alive, September 1958, 13433 died in 1953 and 18061 died in 1950

It is well worthwhile to attempt to determine as accurately as possible the renal threshold for sugar in those patients suspected of having renal glycosuria Using strict criteria, this should, of course, be below 100 milligrams per 100 cc of blood (capillary or arterial) In 4 patients studied by Steinitz[28] the value ranged from 52 to 80 milligrams per 100 cc. The daily excretion of urinary sugar in these patients was as great as 30 to 50 grams Thomas and Southworth[29] carried out detailed studies on a woman, aged twenty-nine years, with whom specimens of urine obtained every fifteen minutes continued to show sugar even after the blood sugar had fallen to 56 mg per cent In this patient the diuresis resulting from the fore-

the incomplete reabsorption of sugar by the renal tubules This in turn may be due to some deviation from the average normal in connection with

the ren

nane

Fr

flow

glycosuria The lessened tubular reabsorption of glucose did not seem to be due to an organic kidney defect because at levels of plasma glucose above 200 mg per cent, the efficiency of tubular reabsorption of glucose equalled or exceeded that found in persons without glycosuria

Treatment of renal glycosuria is unnecessary, although it seems reasonable to urge the patient to eat sparingly of candy, actual sugar, pastry, and to avoid dietary excesses in general Otherwise a liberal and varied diet

[24] Hjärne Acta med Scandin, 67, 422, 1927
[25] Houston and Merrivale Guy's Hosp Reports, 98, 233, 1949
[26] Marble Loc cit, p 721
[27] Lawrence Brit Med Jour, 1, 196, 1929
[28] Steinitz Loc cit p 160
[29] Thomas and Southworth Ann Int Med, 12, 1560, 1939
[30] Friedman, Selzer, Sugarman and Sokolow Am Jour. Med Sci, 204, 22, 1942

the years he has restricted his diet little, if any. October 23, 1958, he was operated upon for cancer of the prostate.

Robbers and Rümelin[17] also believe that renal glycosuria does not progress to diabetes They reported observations in 60 patients with renal glycosuria observed over 2 to 30 years (in most cases over 8 years). None of these had developed diabetes.

It seems reasonable that if one could follow for a period of years a sufficiently large group of individuals with a very low renal threshold for sugar, some of them possessing certain favoring influences, such as obesity and the presence of diabetes in relatives, would develop diabetes mellitus

likewise regard renal glycosuria and diabetes as two distinct conditions which have nothing to do with each other; they consider the prognosis of

lack of connection between the two.

It has been stated that renal glycosuria may be a temporary condition and that a normal renal threshold for sugar may be regained. This happens in the disappearance of the renal glycosuria of pregnancy seen following delivery and in the recovery from phloridzin intoxication. However, in our experience, in true idiopathic renal glycosuria, the condition is permanent if allowance be made for the influence of bodily changes, such as those

with renal glycosuria over a period of years a tendency toward elevation of the renal threshold may become apparent. In recent years such a shift

was removed because of long-standing pyelonephritis, the low renal threshold was abolished

Brown and Poleshuck[22] point out the familial nature of renal glycosuria and report 4 cases occurring in three generations of one family Falta[23] mentions a *family in which 6 of 7 children have renal glycosuria.* He cites

[17] Robbers and Rumelin Deutsch med Wchnschr, *78*, 1321, 1953
[18] Soisalo Acta Soc Med Fenn Duodecim, *14*, 1, 1931
[19] Lawrence Brit Med Jour, *1*, 766, 1940
[20] Schnell Acta med Scandin, *92*, 153, 1937
[21] Callaway Ann Int Med, *33*, 243, 1950
[22] Brown and Poleshuck Jour Lab and Clin Med., *20*, 605, 1935
[23] Falta P 37, loc cit, p 79

(or, more strictly, melituria) One naturally speculates as to the mechanism by which sugar appears in the urine in these patients Obviously such must come about either by transient increases in the blood sugar above the "renal threshold" characteristic for the individual or by diminution in tubular reabsorption Table 141 was not arranged with this thought in mind but as one looks over the various categories, one might well postu-

TABLE 141 —TYPES OF "UNCLASSIFED" MELITURIA.

(*a*) Glycosuria accompanying activity of glands of internal secretion other than the pancreas (1) In hyperthyroidism (2) In hyperpituitarism (3) In conditions in which the suprarenal glands are stimulated

(*b*) Glycosuria due to stimulation of intracranial nerve centers (1) *Piqûre diabetique* of Claude Bernard (2) Brain tumors (3) Cerebral hemorrhage (4) Injuries of the skull

(*c*) Alimentary glycosuria (1) "Glycuresis" (Benedict) (2) Alimentary glycosuria (3) Hunger glycosuria

(*d*) Glycosuria accompanying infections, toxemias, anesthesia and asphyxia

(*e*) Glycosuria in chronic or degenerative conditions (1) Vascular hypertension (2) Chronic nephritis and nephrosis (3) Chronic hepatic disease as cirrhosis of the liver (4) Malignant disease

(*f*) Glycosuria due to chemical agents (1) Phloridzin (2) Poisoning as by uranium, curare, carbon monoxide, caffeine, diuretin, morphine, strychnine, chromic salts, bichloride of mercury and chloroform

(*g*) Melituria other than glycosuria (1) Pentosuria (2) Lactosuria (3) Galactosuria (4) Levulosuria (5) Sucrosuria (See page 199) (6) Mannoheptulosuria (See page 199)

sugar in the urine The normoglycemic glycosuria of pregnancy has not been included under this heading, although it has been suggested that the underlying cause may be transient (anatomical or functional) hypertrophy of the pituitary[39] or overactivity of the thyroid gland[40]

(1) *Hyperthyroidism* —Glycosuria is a frequent and well recognized
acco
beer
lowi

Cushing
Company, p
John
Fitz
Andersen Studies on Blood Sugar and Glycosuria in Exophthalmic Goiter, Copenhagen, Levin & Munksgaard, 1933

should be encouraged It is important that during the first year of observation the patient report to his physician every three months and thereafter at six- and twelve-month intervals for life. On these occasions, in addition to a general physical examination, the blood and urine should be examined at one hour after an ordinary meal.

GLYCOSURIA OF PREGNANCY.—Sugar is often found in the urine of pregnant and parturient women. Among 500 cases of pregnancy studied by

ment with the statement of Mohnike and Worm[32] that the renal threshold becomes lowest during the nineteenth to thirty-fourth weeks of gestation. Williams and Wills[33] found 5.4 per cent of 640 pregnant women to have sugar in the urine. Richardson and Bitter[34] reported that 20 per cent of 247 pregnant women had gross sugar in the urine following an intake of 1.75 grams of glucose per kilogram of body weight without abnormality of the blood-sugar curve Ninety per cent of the pregnant women showed minimal amounts of glucose in the urine. Frank and Nothmann[35] found that, following the ingestion of 100 grams of glucose by pregnant women, glycosuria without hyperglycemia occurred regularly

within a normal range, it is unlikely that true diabetes is present. In

Chapter 28 It may suffice here to state that every pregnant woman who has sugar in the urine should be carefully studied by means of blood-sugar determinations and kept under close observation during the pregnancy, even though the glycosuria is apparently benign.[37,38] If the glycosuria persists or if blood-sugar values are not unequivocably normal, she should be asked to report every three months during the first year following delivery and therafter yearly or at such intervals as the findings to date may dictate At such visits tests of the blood and urine should be made at one hour after a meal

"Unclass fied glycosuria" in our classifica-

[33] Williams Boston Med and Surg Jour, *193*, 163, 1925
, 762, 1956
, 493, 1929
nd Gynec, *24*, 362, 1932
nschr, *67*, 1433, 1920

1956
, 524, 1957

tarism has been the experience of others [48,49] In his review of the literature, [illegible]

[illegible]

ephrine if the dose be large enough The rise in blood sugar and the consequent excretion of urinary sugar take place by breakdown of glycogen in the liver In addition to this direct glycogenolytic effect, epinephrine influences carbohydrate metabolism through its effect on the pituitary-adrenal axis, (see p 128)

The classical experiments of Cannon and his associates[50] showed that during emotional excitement or pain, epinephrine is secreted into the blood stream in unusual amounts and, as one of the results of this, glycosuria may occur. Folin, Denis and Smillie[51] found that 18 per cent of 33 presumably normal medical students showed sugar in the urine which was passed immediately after an important examination Similar results were obtained with a second group of 36 students at a women's college Cannon and Fiske[52] found that in the urine of 25 members of a football team, immediately after a game sugar was present in 12 instances Five of the 12 positive tests were among substitutes who had not played That hyperglycemia and glycosuria under such circumstances are due largely to the emotional stress and not to the exercise *per se* is shown by the studies of Edwards, Richards and Dill[53] They found that, although in a player on the football field there might be an increase in the blood sugar together with glycosuria, in the same individual when exercising strenuously in the laboratory there was apt to be a decrease rather than an increase in the blood sugar. Thus Levine and his colleagues[54] and Best and Partridge[55] reported the finding of hypoglycemia in runners at the end of a marathon race

Green and Emery[56] found the effect of emotion upon glycosuria considerably less than reported above Following a final written examination, the urine of medical and dental students was tested and of 244 samples only 4, or 1 6 per cent, were definitely positive, while 19, or 7 8 per cent, showed a trace of sugar Divergent results reported by different observers may well reflect [illegible]

(4) *Adrenal Co*[illegible]
steroids on carb[illegible]
summary of the [illegible]
pages 127 to 128 It will suffice here to state that under conditions of stress,

[48] Colwell Loc cit, p 620
[49] [illegible]

[illegible] York, D[illegible]

Ap[illegible]

thalmic goiter, there was obtained in general an increase in the height and length of the blood-sugar curve. In 14 instances the maximum value

tion. In 7 of 26 patients with marked exophthalmic goiter he found sugar in the twenty-four-hour quantity of urine. When single specimens were tested, however, urinary sugar was found in all cases at one time or another. Andersen regards it as likely that the renal threshold for sugar is lowered in hyperthyroidism

In 1926, Wilder[43] reported the results of a study of thyroid disease and ... 923, ... 1.1 ... per-

thyroidism. Wilder stressed the action of hyperthyroidism in decreasing carbohydrate tolerance in the diabetic, but expressed doubt as to whether hyperthyroidism ever precipitates true diabetes except in an individual who already has this condition in a latent form. He, therefore, made a sharp distinction as to the cause and significance of diabetic and non-diabetic glycosuria during thyrotoxicosis.

Goldberg and Luft[44] found evidence of distorted glucose tolerance in about 90 per cent of cases of thyrotoxicosis.

diabetes, it is safer to assume that it is not curable and to regard these instances of "temporary diabetes" in thyrotoxicosis as due to the great burden imposed on the organism by the extra thyroid secretion. Wilder

sugar (venous) is 130 mg. per cent or higher or the postprandial blood sugar is 180 mg per cent or higher

(2) *Hyperpituitarism.*—Davidoff and Cushing[46] reported that about 25 per cent of 100 patients with acromegaly had sugar in the urine. Later Coggeshall and Root[47] reviewed these original 100 cases plus 53 other cases of acromegaly subsequently studied at the Peter Bent Brigham Hospital Among the total of 153 cases Coggeshall and Root found in all 55 patients, or 36 per cent with glycosuria (26, or 17 per cent of the 153 acromegalics had diabetes) This frequent association of glycosuria with hyperpitui-

43 Wilder Loc cit, p 71
44 Goldberg and Luft Acta med Scand, *135*, 1, 1949
45 Joslin and Lahey Loc cit, p 629
46 *Davidoff and Cushing* Loc cit, p 620
47 Coggeshall and Root Loc cit, p 620

tients showed that the abnormality in carbohydrate metabolism was only a temporary affair. No support was given to the theory of traumatic origin of diabetes mellitus. Still less basis for the traumatic production of glycosuria and diabetes is furnished by the statements of the neuro-surgeons, Cushing and Horrax, who found such complications to be decidedly rare following operations upon the brain. For a more complete discussion see page 75 and the article by Joslin.[62]

(c) ALIMENTARY GLYCOSURIA.—Under this heading mention must first be made of the point, much debated in the past, as to whether normal urine contains traces of sugar. The truth seems to be that normal urine usually contains small amounts (less than 0.1 per cent) of substances which reduce alkaline copper solutions. Whether these reducing substances are actually traces of glucose or are unassimilable end-products of carbohydrate metabolism,[63] though a matter of great theoretical interest, is of little practical importance. The usual Benedict test is not sensitive enough to detect these traces. Froesch, Renold and McWilliams[64] found that in 30 normal subjects the excretion of true glucose, as measured by a glucose oxidase method averaged 72 mg. in 24 hours (range 16–132 mg.) whereas the total reducing substances were 511 mg. (range 242–845 mg.). Significant increases occurred after the administration of carbohydrate-active adrenal steroids.

A consideration of straightforward "alimentary" glycosuria is of more practical value. By extreme carbohydrate overloading, the point may be reached at which even the normal organism cannot cope with the situation and small amounts of sugar may appear in the urine. Normal individuals, however, possess a very high tolerance in this respect. It is only fair to state that Lawrence[65] has criticized the use of the term "alimentary glycosuria" as vague and meaningless. He maintains that the glycosuria found after food can always be shown to be due to some complicating condition.

Alimentary glycosuria requires no treatment except: (1) Care to insure that the diagnosis is correct, (2) medical supervision, (3) tests of the blood and urine at least yearly.

The glycosuria which follows the giving of food to a starving man or animal is due presumably to temporary overloading with carbohydrate of an organism which has not been accustomed to food. Goldblatt and Ellis,[66] from studies on animals and men who were fasted about forty hours, state that the intolerance for carbohydrate is not primarily due to acidosis. However, when such "hunger glycosuria" is accompanied by acidosis, a blood-sugar determination may be necessary to rule out diabetes mellitus, although with the giving of food the acidosis of starvation quickly disappears.

Sakauchi[67] states that he has frequently found glycosuria without hyper-

[62] Joslin: New England Jour. Med., 223, 22, 1940.

[63] Folin and Berglund: Jour. Biol. Chem., 51, 213, 1922. See also Benedict and Osterberg: Ibid., 55, 769, 1923.

[64] Froesch, Renold and McWilliams: Loc. cit., p. 127.

[65] Lawrence: Med. Clin. North America, p. 289, 1947 (March).

[66] Goldblatt and Ellis: Biochem. Jour., 26, 991, 1932.

[67] Sakauchi: Japanese Jour. Biochem., 16, 259, 1932.

the increased secretion from the adrenal medulla may increase the blood sugar and cause glycosuria not only by causing

is seen ... of the adrena ... among other manifestations elevation of the blood sugar and glycosuria so that diabetes mellitus must ... ever, the ... strati ... olism

(b) GLYCOSURIA OF INTRACRANIAL ORIGIN.

... when he showed that needle puncture in the floor of the fourth ventricle in dogs caused transient glycosuria. The mechanism is commonly held to be that of ... hypothalamus with in turn an effect

The glycosuria accompanying var ... creased intracranial pressure, or in which there exists the possibility of local irritation of nerve centers, may possibly be due to stimulat...

... was reported by Courts.[59] Mader[60] found that injection of air for encephal... gave rise to the s... tures. The hype...

Davidson and ... with concussion of the brain and in 18 patients with fracture of the skull ...

... much higher than corresponding values in normal individuals. Furthermore, ...

[57] Colwell. Loc. cit., p. 620 ... and Psychiat., 13, 335, 1925

Sugar frequently appears in the urine following anesthesia with ether and chloroform The action is due, at least in part, to the acidosis produced by the anesthesia. McKittrick and Root[73] have shown that in the diabetic, during anesthesia produced by ether or nitrous oxide and oxygen, the carbon dioxide combining power of the blood falls and the sugar in the blood increases This is true to a lesser extent when ethylene is used as an anesthetic and still less when spinal anesthesia is used Best *et al.*[74] found that the blood of a dog under ether anesthesia contained only one-tenth the amount of insulin per unit of volume as that of a normal dog

(*e*) Glycosuria in Chronic or Degenerative Conditions.—There are various types of glycosuria met with in everyday practice other than those already mentioned In patients with hypertension, nephritis, or nephrosis, slight glycosuria is not infrequently encountered. Thus, Hiller[75] indentified the presence of dextrose in the urine of patients with kidney disease, thereby confirming the earlier observation that fermentable reduc- [illegible]

kidney damage, although in cases of essential hypertension the influence of overactivity of the sympathetic nervous system must be considered. Brush[76] calls attention to non-diabetic glycosuria in older individuals especially in those who have had some type of obstructive uropathy.

The glycosuria which occasionally accompanies chronic disease of the liver probably arises through impairment of the normal processes of glycogenesis and glycogenolysis in that organ

The question as to why patients with cancer not infrequently show small amounts of sugar in the urine has received considerable attention. On studying these patients it is often found that, although blood sugar values may be normal one hour after an ordinary meal, sugar tolerance curves often show definite deviations from the normal [77, 78] Since the symptomatology characteristic of diabetes is commonly lacking, the most that one can say is that these individuals have an impaired carbohydrate tolerance [illegible] Jackson[81] [illegible] alignancy [illegible] were not consistent enough to be of much help In a paper on "Diabetes and Cancer,"[82] this subject was discussed at length

(*f*) Glycosuria Due to Chemical Agents —The glycosuria due to phloridzin poisoning has no practical importance in man. However, as a tool with which to study carbohydrate metabolism phloridzin has yielded

[73] McKittrick and Root Diabetic Surgery, Philadelphia, Lea & Febiger, Chapter IV, 1928

[74] [illegible] 161, 1924

[illegible]

[illegible] Med Sci, 159, 577, 1920.

[illegible]

glycemia in chronically undernourished children. Experimentally he kept young rabbits in a state of undernutrition for weeks. During the first three to five weeks fasting blood sugar values were normal and tolerance

From the third to the fifth week of undernutrition on, sugar tolerance tests ... lly, however, this

... ue days, in 1912, excreted from 296 to 498 milligrams of reducing substances (calculated as glucose) in the twenty-four-hour quantity of urine during the period of starvation. When on the first day after a month of fasting, about 500 grams of carbohydrate were allowed in a relatively short time, the amount of reducing substances in the urine rose for that day to 4441 milligrams. On the two subsequent days the values were 267 and 246 milligrams, respectively.

(d) Glycosuria Accompanying Infections and Toxemias, Anesthesia and Asphyxia.—Patients with acute infections often excrete small

diagnosis until blood-sugar tests have been carried out. Careful tests of blood and urine should be made after the subsidence of the infection and at three-month intervals during the first year thereafter.

Federer's[69] patient with acute meningitis exhibited transient hyperglycemia, acetonuria and glycosuria. Ferguson and Barr[70] found transient glycosuria in 30 per cent of 72 cases of meningitis admitted to the New York Hospital over a four-year period Of the 13 glycosuric cases in which

dextrose Strauss[72] has shown that the toxemia produced in rabbits by the intravenous injection of streptococcus filtrates definitely lowered the glucose tolerance This effect was not obtained when the toxic filtrate was mixed with an excess of erysipelas antiserum before injection.

It is not surprising that glycosuria should be present during infections since they definitely make true diabetes temporarily more severe In the laboratory it has been abundantly shown that insulin efficiency is lowered by infections and toxemias For further discussion see Chapter 16.

[68] Benedict A Study of Prolonged Fasting, Washington, The Carnegie Institute, p 292, 1915

[69] Federer New England Jour Med, 233, 342, 1945

[70] Ferguson and Barr Ann Int Med, 21, 173, 1944

[71] Williams and Dick Arch Int Med, 50, 801, 1932

[72] Strauss Loc cit, p 165.

Sugar frequently appears in the urine following anesthesia with ether and chloroform. The action is due, at least in part, to the acidosis produced by the anesthesia McKittrick and Root[73] have shown that in the diabetic, during anesthesia produced by ether or nitrous oxide and oxygen, the carbon dioxide combining power of the blood falls and the sugar in the blood increases This is true to a lesser extent when ethylene is used as an anesthetic and still less when spinal anesthesia is used Best *et al*[74] found that the blood of a dog under ether anesthesia contained only one-tenth the amount of insulin per unit of volume as that of a normal dog.

(*e*) Glycosuria in Chronic or Degenerative Conditions.—There are various types of glycosuria met with in everyday practice other than those already mentioned. In patients with hypertension, nephritis, or nephrosis, slight glycosuria is not infrequently encountered Thus, Hiller[75] indentified the presence of dextrose in the urine of patients with kidney [illegible]

kidney damage, although in cases of essential hypertension the influence of overactivity of the sympathetic nervous system must be considered Brush[76] calls attention to non-diabetic glycosuria in older individuals especially in those who have had some type of obstructive uropathy.

The glycosuria which occasionally accompanies chronic disease of the liver probably arises through impairment of the normal processes of glycogenesis and glycogenolysis in that organ

The question as to why patients with cancer not infrequently show small amounts of sugar in the urine has received considerable attention On [illegible]

say is that these individuals have an impaired carbohydrate tolerance Certain clinicians, among them Rohdenburg,[79] Friedenwald[80] and Jackson[81] attempted to find a sugar tolerance curve characteristic of malignancy which might be used for diagnosis in doubtful cases, but results were not consistent enough to be of much help In a paper on "Diabetes and Cancer,"[82] this subject was discussed at length.

(*f*) Glycosuria Due to Chemical Agents —The glycosuria due to phloridzin poisoning has no practical importance in man However, as a tool with which to study carbohydrate metabolism phloridzin has yielded

[73] McKittrick and Root Diabetic Surgery, Philadelphia, Lea & Febiger, Chapter IV, 1928

[74] Best [illegible] ol, *65*, 161, 1924

[illegible] t p 579

[79] Rohdenburg, Bernhard and Krehbiel Am Jour Med Sci, *159*, 577, 1920

[80] Friedenwald and Grove Ibid, *163*, 33, 1922

[81] Jackson Texas State Jour Med, *24*, 622, 1929

[82] Marble Loc cit, p 580.

results of such fundamental importance that the glycosuria produced by this agent requires some comment [83,84,85] Follow... into ar... so that... there results without hyperglycemia a continuous excretion of sugar in the urine. The condition thus mimics quite closely the spontaneously arising renal glycosuria in man. Evidence is lacking that phloridzin poisoning produces noteworthy metabolic changes other than the effect on the kidney

In the course of poi... gly... mo... of mercury, chloroform, uranium salts, ferric compounds[86] and potassium dichromate [87,88]

Lichtwitz[87] states that caffeine, diuretin, morphine, strychnine and chloroform cause glycosuria by stimulation of the central nervous system, whereas curare, carbon monoxide and heavy metals (particularly uranium) act peripherally, probably on the liver cells Hepler and Simonds[88] found some degree of correlation between the glycosuria due to chemical poisoning and: (a) the necrosis of tubular epithelium, (b) albuminuria and (c) the chemical agent and its dose

D. MELITURIA OTHER THAN GLYCOSURIA

In the study of a patient who shows sugar in the urine despite normal blood-sugar values, it is important to ascertain the type of sugar which is excreted In the overwhelming majority of cases the sugar will be found to be glucose, but in a number large enough to make it definitely worthwhile one can succeed in demonstrating that the sugar is not glucose but instead pentose, fructose, or some other sugar less commonly encountered In such cases a systematic study is necessary and in carrying this out the following procedures are valuable·

1. The Benedict Test. This is positive for all sugars which may be found in the urine. Lasker and Enklewitz[89] have called attention to the fact that with urine containing pentose, reduction of the copper solution takes place after a few hours at room temperature (i e, without heating) and within ten minutes at 50° to 60° C. Fructose (levulose), also a ketose, reduces Benedict's solution quickly at 50° to 60° C. but much more slowly than pentose at temperatures below 40° C. Like pentose and fructose, mannoheptulose reduces Benedict's solution in the cold [90]

2 Glucose oxidase test This is specific for glucose

3 Fermentation with baker's yeast Glucose and fructose are always,

galactose usually, lactose occasionally, pentose and mannoheptulose never fermented

methyl-phenylhydrazine (the latter in the case of levulose) can be obtained. This test should be carried further by determining the melting-point of these

with spe-
(phloro-
tose and
galactose and polariscopic and spectroscopic examinations These are described in Chapter 7 and by Trumper and Cantarow.[92] Exton[93]

temperature of a bath constant and noting the presence or absence of reduction after certain stated intervals of time, differentiation of the reducing sugar is possible.

Chronic Essential Pentosuria.—Chronic essential pentosuria is a rare, benign condition belonging in the group of "inborn errors of metabolism," characterized by the constant presence in the urine of small quantities of pentose, usually *l*-xylulose All reported cases have been in Jews and predominantly in males The condition is harmless, asymptomatic and has no relation to diabetes mellitus.

intermediate in this pathway is *l*-xylulose, the sugar which appears in the urine of patients with congenital pentosuria Normally, this sugar is converted to the sugar alcohol, xylitol, which may then be transformed through a series of intermediates to hexose Recent evidence indicates that the enzyme responsible for the conversion of *l*-xylulose to xylitol may be deficient in individuals with pentosuria Because *l*-xylulose cannot be further metabolized in pentosuria, it is excreted in the urine "[94,95]

Salzman[96] reported the case of a Jewish girl, aged seventeen years, in whom melituria of thirteen years' standing was shown to be due to the excretion of pentose One of Neuman's[97] 4 cases had been observed for twenty-seven years Two of the 3 cases reported by us in 1932[98] are alive

[91] Castellani Jour State Med, *39*, 621, 1931
[92] Trumper and Cantarow Internat Clin, 41st Series, *1*, 38, 1931
[93] Exton Loc cit p 107
[94] Hiatt Biochim Biophys Acta, *28*, 645, 1958
[95] Touster, Hutcheson and Rice Jour Biol Chem, *215*, 677, 1955
[96] Salzman Jour Am Med Assn, *103*, 483, 1934
[97] Neuman Med Ann Dist Columbia, Washington, *1*, 79, 1932, Abstract, Jour Am Med Assn, *99*, 1546, 1932
[98] Marble Am Jour Med Sci, *183*, 827, 1932

in 1958, following no treatment directed toward the melituria. Case 7995 died in 1949, twenty-four years after the first observation of urinary sugar. Enklewitz and Lasker[99,100] reported the occurrence in twins of pentosuria of known duration of seventeen years. The cases had previously been regarded by others as instances of juvenile diabetes, and later of renal diabetes in twins. Derivaux[101] in 1943 found a total of 163 cases of pentosuria reported in the literature. Blatherwick[102] quoted Margolis[103] as finding 11 cases of pentosuria in 22,000 urine examinations, and stated his own experience in which the incidence was about 1 to 50,000 examinations carried out in connection with applications for life insurance.

Our own series includes 11 patients with chronic essential pentosuria, Cases 1473, 1484, 6629, 6760, 7995, 13676, 16923, 18070, 18217, 30835 and 44095 All of these patients are Jewish, ranging in age from 2 8 to 31.6 years at the time of the first discovery of sugar, and all but Cases 1484 and 6629 are males. As stated above Case 7995 has died. All others are in good health and have shown no tendency toward progression to diabetes, despite the fact that melituria has been known to exist for at least 15 years and in 5 cases (1473, 1484, 6629, 6760, 7995) for twenty years or more.

It is stated that transient pentosuria occurs after large quantities of certain fruits, as plums, cherries, grapes and prunes, have been eaten. Pentose is also said to occur in the urine along with glucose in certain cases of diabetes mellitus

Enklewitz and Lasker[104] in reporting 12 cases of true chronic essential pentosuria, quote W. Voit as obtaining an osazone with the melting-point of a pentosazone from the urine of 1[illegible]
selves in the examination of the uri[illegible]
to obtain a single positive reaction [illegible]
tered one case (Case 6629) of pentosuria in a patient who, on the basis of [illegible] This young [illegible]

and further study

By the systematic examination of urine specimens of large groups of high school students and by contacts with physicians, Lasker[105,106] identified more than 70 cases of pentosuria, in all of these the sugar excreted was *l*-xyloketose Lasker questions the validity of reports in the earlier literature in which the sugar excreted was said to have been arabinose. There is no doubt but that pentosuria is inherited, apparently as a Mendelian recessive trait It seems likely that most of the families of pentosurics, at least those in the New York area as studied by Lasker, came from foci of rela-

suria, 2 of the patients were brothers and one of these had 2 sons with pentosuria In a related branch of the family there were 7 instances of renal glycosuria plus 1 case of glycosuria of pregnancy The pentose was identified as *l*-xylulose. Schultsz believes that pentosuria is transmitted as a dominant trait.

Lactosuria.—Lactosuria has already been mentioned in the discussion

found in standard texts and in an article by Trumper and Cantarow [109]

Watkins[110] carried out an extensive study of lactose metabolism in women. *She found that during the last stages of pregnancy there is a*

immediatly drops to a low level where it remains for from two to five days with then a sudden and often tremendous excretion of lactose Watkins gives in detail the method for determination of lactose in urine

Tolstoi[111] found that in diabetic, lactating women, the concentration of lactose in the breast milk remained remarkably constant in spite of very marked elevations or depressions of the blood glucose concentration

Galactosuria.—Spontaneous galactosuria is of little importance in clinical medicine One test of liver function is based on the ability of that organ to metabolize a certain amount of galactose (40 grams given orally) Normally 3 grams or less are excreted in the urine within five hours Ex-

liver and spleen, anemia, and albuminuria Cataracts may develop and mental retardation may be present Cases have been described by Mason and Turner,[112] Norman and Fashena[113] and by Bell *et al* [114] Relief from the condition may be secured by removing milk from the diet As stated by

[107] Macumber Jour Okla Med Assn, *42*, 281, 1949
[108] Schultsz Onderzoekingen over Pentosurie, Amsterdam, N V Uitgevers-Maatschappij, "Kosmos," 1938
[109] Trumper and Cantarow Loc cit p 733
[110] Watkins Loc cit, p 724
[111] Tolstoi Jour Clin Invest, *14*, 863, 1935
[112] Mason and Turner Am Jour Dis Child, *50*, 359, 1935
[113] Norman and Fashena Ibid, *66*, 531, 1942 see also the article by Bruck and Rapoport Ibid, *70*, 267, 1945
[114] Bell, Blair, Lindsay and Watson Jour Pediat, *36*, 427, 1950 Idem Arch Path, *49*, 393, 1950

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Anast and Jackson,[115] present evidence suggests that galactosemia is a genetically determined disease in which a specific enzyme is lacking.

For the identification of galactose in the urine the reader is referred to standard laboratory texts.

Fructosuria (Levulosuria).—Essential fructosuria is a rare condition.

Case 15117, female 1.3 years in July, 1932; and Case 21113, female, 18.0 years in November, 1941. Cases 13228 and 21113 are brother and sister. All are living and well in 1958. Studies of Case 13228 were reported in detail.[116] We are indebted to Mrs. Margaret Lasker of New York for demonstrating the existence of fructosuria in Case 7157.

Writing in 1937, Blatherwick[117] stated that only 34 cases of essential fructosuria had been recorded in the literature up until that time. Nine of these case reports were by American authors, the first by Strouse and Friedman[118] in 1912, a Dutch case described by Heeres and Vos[119] in 1929, 6 others by Silver and Reiner[120] in 1934, and 1 by Marble and Smith[121] in 1936. Blatherwick[122] mentioned that he had studied the metabolism in 2 cases of fructosuria occurring in a sister and a brother. Jacobsen's[123] patients were brothers. Careful studies yielded no evidence of diabetes in the 20 year old soldier reported by Lenzner[124] although his mother and maternal grandmother were diabetic.

In individuals with essential fructosuria, the rate at which fructose is removed from the blood stream is retarded, presumably because of impaired liver function. As a consequence, a blood fructose level well above the kidney threshold is temporarily maintained and fructosuria results. The condition is harmless and requires no treatment.

In connection with a detailed study of 3 patients with essential fructosuria, Soisalo[125] carried out fructose tolerance tests on 3 healthy persons,

the level just mentioned. In one normal subject studied by us the renal threshold for fructose seemed to be about 11 mg. per cent.

Levulose as well as dextrose is said to occur in the urine in severe cases of diabetes mellitus. Our experience affords but little data on this point, although in Case 12377, a young Jewish woman with mild diabetes, aged

associated with glucose in the urine. Studies in this case were reported[126] The patient died July 13, 1938 of cirrhosis of the liver

E PROGNOSIS IN NON-DIABETIC GLYCOSURIAS

What is the likelihood that an individual with apparently benign glycosuria may subsequently develop diabetes? As has been mentioned previously, in 1937 a study was made of 2065 patients who in thirty-eight years between 1897 and 1935 came because of glycosuria which at the time of the

traced Careful preliminary examination of the records led to the discarding of certain cases so that actually 1946 cases were used as the basis of the study. Of these, 1142 were males and 804 females One thousand six hundred thirty-six patients were living and 310 were dead In 193 cases, or 9 9 per cent of the total, true diabetes had developed, which in most instances was mild

The features favoring the development of diabetes were, in approximately the order named: advancing age, overweight, blood-sugar values

gh below a definitely
history of diabetes
asing duration since

initial observation It was higher in Jewish than in non-Jewish patients Adequate study at initial observation, particularly with postprandial blood-sugar tests and glucose tolerance tests, increased greatly the chances of

annum in patients inadequately studied

A survey of the types of melituria which has been made may seem at first thought to indicate that a complicated and difficult diagnostic problem presents itself whenever sugar is found in the urine Such is not the case Unusual cases there will be, and at times it may be difficult to state whether a given patient has, or has not, diabetes Usually, however, a few simple guiding principles will suffice to establish a satisfactory diagnosis In general, the proper sequence of action in any case should be as follows

1 A proper evaluation of the patient's history physical examination and his hereditary background

2 Examination of the urine for sugar before and after a meal

3 Determination of the percentage of sugar in the blood at one hour after a meal liberal in carbohydrate

4 In doubtful cases, the carrying out of a sugar tolerance test

5 In cases of persistent melituria despite normal blood-sugar values, the identification of the type of sugar excreted.

Such tests should be carried out promptly, once the problem of diagnosis

[126] Marble and Smith Loc. cit., p 736

has presented itself. An opini- . . .
able. Delay provokes
. . . t the melituria
. . . o diet and living
. . . suggested earlier in this chapter. In any case, however, the patient should be kept under observation and requested to report every three months for the first year and at yearly or twice yearly intervals thereafter until such visits no longer seem necessary. On these occasions examinations of the urine and blood for sugar should be made one hour after a meal liberal in carbohydrate.

APPENDIX A

We are indebted to Mrs Elizabeth K. Caso, Nutritionist in the United States Public Health Service, for the preparation of the following dietary data.

For foods consumed in Central America reference is made to: "Tabla de Composicion de Alimentos de Centro America y Panama," 3rd ed., Publicaciones Cientificas del Instituto de Nutricion de Centro America y Panama, San Salvador, El Salvador, Centro America, 1955

NEW METHOD OF CALCULATING DIABETIC DIETS

A joint committee of the American Diabetes Association, American Dietetic Association, and Diabetes Section, Public Health Service, after

TABLE 142.—FOOD VALUES FOR CALCULATING DIABETIC DIETS

Group	Amount	*Weight gm*	*Carb gm*	*Protein gm*	*Fat gm*	*Energy calories*
Milk, whole (List 1)	½ pint	240	12	8	10	170
Vegetable (List 2A)	as desired	-	—		—	—
Vegetable (List 2B)	½ cup	100	7	2	-	36
Fruit (List 3)	varies	—	10		-	40
Bread Exchanges (List 4)	varies	-	15	2	-	68
Meat Exchanges (List 5)	1 oz	30	—	7	5	73
Fat Exchanges (List 6)	1 tsp	5	—	-	5	45

Foods of similar composition have been combined into "six food exchange lists." These lists are presented below.

MILK EXCHANGES LIST 1

One exchange contains Carbohydrate 12 grams, protein 8 grams, fat 10 grams 170 calories

	Amount to use
Whole milk (plain or homogenized)	1 cup
*Skim milk	1 cup
Evaporated milk	½ cup
Powdered whole milk	¼ cup
*Powdered skim milk (non-fat dried milk)	¼ cup
Buttermilk (made from whole milk)	1 cup
*Buttermilk (made from skim milk)	1 cup

* Skim milk products contain less fat. When exchanged for whole milk add two fat exchanges to get the same food value.

[1] Revised Table of Food Values, Proc. Am. Diabetes A., 9, 403, 1949.
[2] Caso, J. Am. Dietet. Assn. 26, 575, 1950.

Vegetable Exchanges List 2

Vegetable exchanges A contains: negligible amounts of carbohydrate, protein, and fat. In raw form, size of serving unlimited; cooked, size serving ½ to 1 cup

Asparagus	*Escarole	Mustard	Sauerkraut
*Broccoli	Eggplant	Spinach	String beans, young
Brussels sprouts	*Greens	Turnip greens	Summer squash
Cabbage	*Beet greens*	*Lettuce*	**Tomatoes—1 per serving*
Cauliflower	Chard	Mushrooms	*Watercress
Celery	Collard	Okra	
*Chicory	Dandelion	*Pepper	
Cucumbers	Kale	Radishes	

Vegetable exchanges B contains carbohydrate 7 grams, protein 2 grams 35 calories. One serving equals ½ cup

Beets	Pumpkin
*Carrots	Rutabagas
Onions	*Squash, winter
Peas, green	Turnip

* Contains considerable amount of vitamin A

Fruit Exchanges List 3

One exchange contains carbohydrate 10 grams 40 calories Fruits may be fresh, dried, cooked, canned or frozen as long as no sugar is added

	Amount to Use		*Amount to Use*
Apple (2" dia)	1 small	Grapes	12
Applesauce	½ cup	Grape juice	¼ cup
Apricots, fresh	2 medium	Honeydew melon, medium	⅛
Apricots, dried	4 halves	Mango	½ small
Banana	½ small	*Orange	1 small
Blackberries	1 cup	*Orange juice	½ cup
Raspberries	1 cup	Papaya	⅓ medium
*Strawberries	1 cup	Peach	1 medium
Blueberries	⅔ cup	Pear	1 small
*Cantaloupe (6" dia)	¼	Pineapple	½ cup
Cherries	10 large	Pineapple juice	⅓ cup
Dates	2	Plums	2 medium
Figs, fresh	2 large	Prunes, dried	2 medium
Figs, dried	1 small	Raisins	2 tablespoons
*Grapefruit	½ small	*Tangerine	1 large
*Grapefruit juice	½ cup	Watermelon	1 cup

* Contains considerable amount of vitamin C (ascorbic acid)

Bread Exchanges List 4

One exchange contains carbohydrate 15 grams, protein 2 grams 70 calories

	Amount to Use
Bread	1 slice
Biscuit, roll (2" dia.)	1
Muffin (2" dia)	1
Cornbread (1½" cube)	1
Cereals, cooked	½ cup
Dry, flake & puff types	¾ cup
Rice, grits, cooked	½ cup
Spaghetti, noodles, cooked	½ cup
Macaroni, etc , cooked	½ cup
Crackers, graham (2½" sq)	2
Oyster (½ cup)	20
Saltines (2" sq)	5
Soda (2½" sq)	3
Round, thin	6
Flour	2½ tablespoons
Vegetables	
Beans and peas, dried, cooked (lima, navy, split pea, cowpeas, etc)	½ cup
Baked beans, no pork	¼ cup
Corn	⅓ cup
Popcorn	1 cup
Parsnips	⅔ cup
Potatoes, white	1 small
Potatoes, white, mashed	½ cup
Potatoes, sweet or yams	¼ cup
Sponge cake, plain (1½" cube)	1
Ice cream (omit two fat exchanges)	½ cup

Meat Exchanges List 5

One exchange contains Protein 7 grams, fat 5 grams 75 calories

	Amount to Use
[illegible]	1 ounce
[illegible]	1 slice
[illegible] wurst, luncheon loaf	
Frankfurter (8–9 per lb)	1
Egg	1
Fish Haddock, etc	1 ounce
Salmon, tuna, crab, lobster	¼ cup
Shrimp, clams, oysters, etc	5 small
Sardines	3 medium
Cheese, Cheddar type	1 ounce
cottage	¼ cup
Peanut butter	2 tablespoons

NOTE Three meat exchanges are usually prescribed for the main meal of the day This would be equal to ¼ lb of meat or fish (raw weight) or three servings of any of the items listed above

Fat Exchanges List 6

One exchange contains: Fat 5 grams: 45 calories.

	Amount to Use		Amount to Use
Butter or margarine	1 teaspoon	French dressing	1 tablespoon
Bacon, crisp	1 slice	Mayonnaise	1 teaspoon
Cream, light	2 tablespoons	Oil or cooking fat	1 teaspoon
Cream, heavy	1 tablespoon	Nuts	6 small
Cream cheese	1 tablespoon	Olives	5 small
Avocado (4" diameter)	⅛		

Table 143.—Total Day's Food

Carbohydrate 150 Gm., protein 70 Gm., fat 70 Gm.
Calories 1500

List 1	Milk, 1 pint
List 2A	Vegetables, as desired
List 2B	Vegetables, 1 serving
List 3	Fruits, 3 servings
List 4	Bread Exchanges, 6 servings
List 5	Meat Exchanges, 6 servings
List 6	Fat Exchanges, 4 servings

Select each day one green or yellow vegetable. One fruit or vegetable should be a good source of vitamin C.
This food may be divided into meals as follows.

SAMPLE MENU

Breakfast
- Orange Juice—½ cup
- Egg—1
- Toast—1 slice Butter—1 teaspoon
- Coffee—2 tablespoons light cream

Lunch or Supper
- Ham and Cheese Sandwich (Cheese—1 ounce, Ham—1 ounce, Bread—2 slices, Butter—1 teaspoon)
- Lettuce and Tomato Salad
- Apple—1 small
- Milk—1 cup (8 ounces)
- Coffee or Tea

Dinner:
- Hamburg Patties—3 ounces
- Mashed Potato—½ cup
- Carrots—½ cup Spinach
- Bread—1 slice Butter—1 teaspoon
- Banana—½ small
- Coffee or Tea

Bedtime
- Milk—1 cup (8 ounces)
- Graham Crackers—2

SAMPLE MEAL PLAN

Breakfast	
Fruit, 1 serving	List 3
Egg, or other meat exchange	List 5
Bread, 1 exchange	List 4
Butter, 1 level teaspoon or other fat exchange	List 6
Tea or coffee	As desired
Lunch or supper	
Meat, 2 exchanges	List 5
Bread, 2 exchanges	List 4
Vegetables, as desired	List 2A
Fruit, 1 serving	List 3
Milk, 1 cup	List 1*
Butter, 1 level teaspoon or other fat exchange	List 6
Tea or coffee	As desired
Dinner or main meal	
Meat, 3 exchanges	List 5
Bread, 2 exchanges	List 4
Vegetables, as desired	List 2A
Vegetables, 1 serving, ½ cup	List 2B
Fruit, 1 serving	List 3
Butter, 1 level teaspoon or other fat exchange	List 6
Tea or coffee	As desired
Bedtime	
Milk, 1 cup	List 1*
Bread, 1 exchange	List 4
Butter, 1 level teaspoon or other fat exchange	List 6

* Part of milk may be used in morning for coffee or for cereal when selected as a bread exchange.

APPENDIX B

TABLE 144 —COMPOSITION OF FOODS, 100 GRAMS EDIBLE PORTION*

(Extracted by permission from Watt and Merrill Composition of Foods, United States Department of Agriculture Handbook No 8, 1950)

Food and description	Food energy Cal	Protein Gm	Fat, Gm	Carbohydrate Total, Gm	Calcium, Mg	Iron, Mg	Vitamin A value, I U.	Thiamine, Mg	Riboflavin, Mg	Niacin, Mg	Ascorbic acid, Mg
Almonds dried unblanched	597	18 6	54 1	19 6	254	4 4	0	0 25	0 67	4 6	Trace
Apples Raw	58	3	4	14 9	6	3	90	04	03	2	5
Applesauce canned Unsweetened	42	2	2	10 9	4	4	30	02	01	Trace	1
Apricots											
Raw	51	1 0	1	12 9	16	5	2,790	03	05	8	7
Canned											
Water pack solids and liquid	32	5	1	8 1	10	3	1,350	02	02	3	4
Frozen	82	7	1	21 0	11	4	1,660	02	03	5	4
Asparagus cooked	20	2 4	2	3 6	19	1 0	1 040	13	17	1 2	23
Avocados raw[1]	245	1 7	26 4	5 1	10	6	290	06	13	1 1	16
Bacon medium fat											
Broiled or fried drained	607	25	55	1	25	3 3	(0)	48	31	4 8	0
Bananas raw	88	1 2	2	23	8	6	430	04	05	7	10
Beans common or kidney mature dry seeds											
Red kidney Raw dry	336	23 1	1 7	59 4	163	6 9	(0)	57	22	2 5	2
Canned (or cooked) solids and liquid	90	5 7	4	16 4	40	1 9	(0)	05	05	8	0
Other (including navy pea white marrow, other)											
Canned, baked Pork and molasses	125	5 8	3 0	19 2	56	2 1	30	05	04	5	2
Beans, lima, Immature seeds cooked	95	5 0	4	18 3	29	1 7	290	14	09	1 1	15
Beans, snap											
Green Cooked (small amount of water, short time)	22	1 4	2	4 7	36	7	600	07	10	5	14
Wax or yellow Canned											
Solids and liquid	18	1 0	1	4 2	27	1 4	100	03	04	3	4
Drained solids	22	1 4	2	4 7	36	1 7	120	04	05	4	5
Beef cuts, medium fat											
Chuck Cooked	309	26	22	0	11	3 1	(0)	05[2]	20[2]	4 1[2]	0
Hamburger Cooked	364	22	30	0	9	2 8	(0)	08	19	4 8	0

* Asterisk indicates that values are calculated from a recipe parentheses indicate imputed value

[1] Data on proximate constituents apply to Fuerte variety

[2] Data assume cut to be prepared by braising or not roasting Use of proportionate quantity of drippings would add approximately 50 per cent more thiamin and niacin and 25 per cent more riboflavin

TABLE 144.—COMPOSITION OF FOODS, 100 GRAMS, EDIBLE PORTION *—(Continued)

Food and description	Food energy, Cal	Protein, Gm	Fat, Gm	Carbohydrate Total, Gm	Calcium, Mg	Iron, Mg	Vitamin A value, I U	Thiamine, Mg	Riboflavin, Mg	Niacin, Mg	Ascorbic acid, Mg
Beef cuts, medium fat											
Porterhouse Cooked	342	23	27	0	11	3.0	(0)	.06	.18	4.7	0
Rib roast Cooked	319	21	24	0	10	3.0	(0)	.06	.18	4.3	0
Round Cooked	234	27	13	0	11	3.4	(0)	.08	.22	5.5	0
Sirloin Cooked	297	23	22	0	10	2.9	(0)	.06	.19	4.8	0
Beef, canned											
Corned beef hash	141	13.7	6.1	7.2	26	1.3	Trace	.03	.14	2.9	0
Beef, corned, boneless											
Canned Medium fat	216	25.3	12	0	20	4.3	(0)	.02	.24	3.4	0
Beef dried or chipped	203	34.3	6.3	0	20	5.1	(0)	(.07)	(.32)	(3.8)	0
Beer (average 4 per cent alcohol)*		.6	0	4.4	4	0	(0)	Trace	.03	.2	(0)
Beets, common red Cooked	41	1.0	.1	9.8	21	.7	20	.02	.04	.3	7
Beet greens, common Cooked	27	2.0	.3	5.6	118	3.2	7440	.05	.16	.4	15
Beverages, carbonated											
Ginger ale	35		—	9	—	—	—	—	—	—	—
Other, including kola type	46			12	—	—	—	—	—	—	—
*Biscuits, baking powder made with											
Enriched flour	342	8.2	10.6	52.2	218	1.8	0	.23	.22	2.0	0
Blackberries											
Raw	57	1.2	1.0	12.5	32	.9	200	.04	.04	.4	21
Canned, solids and liquids											
Water pack	43	.9	.7	9.4	18	(.7)	180	.01	.02	.2	6
Blueberries											
Raw	61	.6	.6	15.1	16	.8	280	(.02)	(.02)	(.3)	16
Bluefish Cooked, baked	155	27.4	4.2	0	23	.7	—	.12	.11	2.2	—
Brains, all kinds raw	125	10.4	8.6	.8	16	3.6	0	.23	.26	4.4	18
Bran (breakfast cereal, almost wholly bran)	242	12.0	3.4	74.2	94	10.3	(0)	.37	.39	19.2	(0)
Bran flakes (40 per cent bran)	292	10.8	1.9	78.8	61	5.1	(0)	.46	.21	8.7	(0)
Brazil nuts	646	14.4	65.9	11.0	186	3.4	Trace	.86	—	—	—
*Breads											
Boston brown bread made with degermed corn meal											
Unenriched	219	4.8	2.1	46.0	185	2.5	140	.08	.12	1.4	0
Cracked-wheat bread, made with											
Enriched flour	259	8.5	2.2	51.4	83	2.0	0	.25	.19	2.5	0
Toasted	299	9.8	2.5	59.5	96	2.3	0	.21	.22	2.9	0

French or Vienna breads											
Enriched	270	9 1	2 7	52 0	24	1 5[5]	0	24[5]	15[5]	2 2[5]	0
Raisin bread											
Unenriched	284	7 1	3 1	57 8	80	1 3	10	07	11	9	0
Toasted	318	7 9	3 5	64 6	89	1 5	10	06	12	1 0	0
Rye bread American (⅓ rye, ⅔ clear flour)	244	9 1	1 2	52 4	72	1 6	0	18	08	1 5	0
White bread unenriched											
4 per cent nonfat milk solids[6]	275	8 5	3 2	51 8	79	6	0	05	11	9	0
Toasted	313	9 7	3 7	59 0	90	7	0	05	12	1 0	0
White bread, enriched											
4 per cent nonfat milk solids[6]	275	8 5	3 2	51 8	79	1 8[5]	0	24[5]	15[5]	2 2[5]	0
Toasted	313	9 7	3 7	59 0	90	2 1	0	22	18	2 5	0
Whole-wheat bread	240	9 3	2 6	49 0	96	2 2	0	30	13	3 0	0
Broccoli flower stalks											
Cooked	29	3 3	2	5 5	130	1 3	3,400	07	15	8	74
Brussels sprouts											
Cooked	47	4 4	5	8 9	34	1 3	400	04	12	5	47
Buckwheat flour											
Dark	347	11 7	2 5	72 0	33	2 8	(0)	58	15	2 9	(0)
Light	348	6 4	1 2	79 5	11	1 0	(0)	08	(04)	(4)	(0)
Butter	716	6	81	4	20	0	3,300[a]	Trace	01	1	0
Buttermilk cultured (made from skim milk)	36	3 5	1	5 1	(118)	1	Trace	04	18	1	1
Cabbage											
Raw	24	1 4	2	5 3	46	5	80	06	05	3	50
Cooked (small amount of water short time)	21	1 4	2	5 3	46	5	90	05	05	3	31
Cabbage, celery or Chinese											
Raw	14	1 2	3	2 4	43	9	260	03	04	4	31
*Cakes											
Fruit dark	351	5 2	13 8	55 9	97	2 8	160[7]	14	14	1 1	(0)
Plain cake and cupcakes	327	6 4	8 2	57 0	155	4	120[7]	03	08	3	(0)
Pound	431	7 1	23 5	49 3	52	1 0	330[7]	12	16	9	(0)
Sponge	291	7 9	5 0	54 4	28	1 4	520	05	15	2	(0)

[3] The value excluding energy derived from alcohol is 20 calories If the energy from alcohol is considered available, the value is 48 calories

[4] Calcium may not be available because of presence of oxalic acid

[5] Iron, thiamine riboflavin, and niacin are based on the minimum level of enrichment specified in standards of identity proposed by the Federal Security Agency and published in the Federal Register, August 3, 1943

[6] When the amount of nonfat milk solids in commercial bread is unknown, use bread with 4 per cent nonfat milk solids, item 135 for unenriched bread and 139 for enriched

[7] If the fat used in the recipe is butter or fortified margarine, the vitamin A value per 100 gm would be 540 I U in foundation cake, 430 I U in foundation cake iced 410 I U in dark fruit cake 370 I U in plain cake, 280 I U in plain cake iced, 990 I U in pound cake, 830 I U in rich cake, and 690 I U in rich cake iced

TABLE 144 COMPOSITION OF FOODS, 100 GRAMS, EDIBLE PORTION *—(Continued)

Food and description	Food energy Cal	Protein, Gm	Fat, Gm	Carbohydrate Total, Gm.	Calcium, Mg	Iron, Mg.	Vitamin A value, I U	Thiamine, Mg.	Riboflavin, Mg	Niacin, Mg	Ascorbic acid, Mg
Candy											
*Butterscotch	410	0	8 9	85 6	20	1 8	(0)	(0)	Trace	Trace	(0)
*Caramels	415	2 9	11 6	77 5	126	2 3	170	02	14	1	Trace
Chocolate, sweetened, milk	503	(6)	33 5	55 7	216	4 0	150	10	38	8	(0)
Chocolate, sweetened, milk with almonds	532	(8)	38 6	50 0	206	2 9	140	13	51	(1 1)	(0)
Chocolate creams	394	4	14	72	—	—	—	—	—	—	(0)
*Fudge, plain	411	1 7	11 3	81 3	48[4]	3	220	01	07	1	Trace
Hard	383	0	0	99	(0)	(0)	(0)	(0)	(0)	(0)	(0)
Marshmallows	325	3	0	81	(0)	(0)	(0)	(0)	(0)	(0)	(0)
*Peanut brittle	441	8 3	15 5	72 8	38	2 0	30	09	05	4 9	0
Cantaloups, raw	20	6	2	4 6	17	4	4203[5]	05	04	5	33
Carrots											
Raw	42	1 2	0 3	9 3	39	0 8	12,000	0 06	0 06	0 5	—
Cooked	30	6	5	6 4	26	6	12,500	05	05	4	4
Cashew nuts roasted or cooked	578	18 5	48 2	27 0	46	5 0	—	63	19	2 1	—
Cauliflower											
Raw	25	2 4	2	4 9	22	1 1	90	11	10	6	69
Cooked	25	2 4	2	4 9	22	1 1	90	06	08	5	28
Celery, bleached											
Raw	18	1 3	2	3 7	50	5	0	05	04	4	7
Cooked	18	1 3	2	3 7	50	5	0	04	03	3	5
Chard, leaves and stalks											
Cooked	21	1 4	2	4 4	105[4]	2 5	3,110	04	06	4	17
Cheese											
Blue mold domestic type	368	21 5	30 5	2 0	315	(5)	(1,240)	03	61	4	(0)
Camembert	299	17 5	24 7	1 8	105	5	(1,020)	04	75	1 1	(0)
Cheddar	398	25 0	32 2	2 1	725	1 0	1,400	02	42	Trace	(0)
Cheddar, processed	370	23 2	29 9	2 0	673	9	(1,300)	02	41	Trace	(0)
Cottage, from skim milk	95	19 5	5	2 0	96	3	(20)	02	31	(1)	(0)
Cream cheese	371	9 0	37 0	2 0	68	2	(1,450)	(01)	22	1	(0)
Swiss	370	27 5	28 0	1 7	925	9	1,450	01	(40)	(1)	(0)
Cherries, sour, sweet, and hybrid, raw	61	1 1	5	14 8	18	4	620	05	06	4	8
Chicken											
Raw											
Broilers, total edible	151	20 2	7 2	0	14	1 5	(0)	08	16	10 2	(0)
Roasters, total edible	200	20 2	12 6	0	14	1 5	(0)	08	16	8 0	(0)
Hens, total edible	302	18 0	25 0	0	14	1 5	(0)	08	16	8 0	(0)

Chili sauce	98	2 8	0 4	23 7	(12)	(0 8)	(1 880)	(0 09)	(0 07)	(2 2)	(11)
Chocolate											
Bitter or unsweetened	501	(5 5)	52 9	29 2[11]	98[10]	(4 4)	60	05	24	1 1	(0)
Sweetened											
Plain	471	(2)	29 8	62 7	(63)[10]	2 8	(30)	(03)	(15)	(6)	(0)
Milk *See* Candy											
Chocolate sirup	209	(1 2)	1 1	56 6	(15)[10]	(1 4)	—	—	—	—	—
Clams, long *and round*											
Raw meat only	81	12 8	1 4	3 4	(96)	(7 0)	110	10	18	(1 6)	—
Cocoa, breakfast plain, *dry powder*	293	(8)	23 8	48 9[11]	125[10]	11 6	(30)	12	38	2 3	(0)
*Cocoa beverage, made with all milk	95	3 8	4 6	10 9	119	4	160	04	19	2	1
Coconut											
Fresh meat	359	3 4	34 7	14 0	21	2 0	0	10	01	2	2
Dried shredded *(sweetened)*	550	3 6	39 1	53 2	43	3 6	0	Trace	Trace	Trace	(0)
Cod											
Raw	74	16 5	4	0	10	4	0	06	09	2 2	2
Dried	375	81 8	2 8	0	(50)	3 6	0	08	45	10 9	(0)
*Coleslaw	56	1 3	6 1	7 7	39	4	70	05	04	2	41
Collards											
Cooked (boiled in small or moderate amount of water until tender)	40	3 9	6	7 2	249	1 6	7 630	08	24	(1 7)	44
Cookies plain and assorted	476	6 0	12 7	75 0	22	6	(0)	04	04	5	(0)
Corn, sweet, white or yellow											
Cooked	85	2 7	7	20 2	5	6	390[13]	11	10	1 4	8
**Corn bread or* muffins made with											
Enriched, degermed corn meal	219	6 7	4 7	36 6	139	1 9	130[14]	17	23	1 3	(0)
Corn *flakes*	385	8 1	4	85 0	11	1 3	(0)	04	10	1 6	(0)
Corn flour	368	7 8	2 6	76 8	6	1 8	340[15]	0 20	0 06	(1 4)	(0)

[8] If the calcium contributed by chocolate is considered unavailable, the value would be *38 mg per 100 gm*

[9] Vitamin A based on deeply *colored varieties*

[10] Calcium may not be available because of presence of oxalic acid

[11] Approximately *one-third of this total amount of* carbohydrate calculated by difference in starch and sugar The remaining portions made up of materials thought to be utilized only poorly if at all by the body

[12] Calcium may not be available because of presence of oxalic acid

[13] Vitamin A based on yellow corn white corn contains only a trace

[14] Based on recipe using white corn meal if yellow corn *meal is used, the* vitamin A value is 250 I U

[15] *Vitamin* A based on yellow corn flour white corn flour contains only a trace

TABLE 144 COMPOSITION OF FOODS, 100 GRAMS, EDIBLE PORTION *—(*Continued*).

Food and description	*Food energy Cal*	*Protein, Gm*	*Fat, Gm*	*Carbohydrate Total Gm*	*Calcium, Mg*	*Iron, Mg*	*Vitamin A value, I U*	*Thiamine, Mg*	*Riboflavin, Mg*	*Niacin, Mg*	*Ascorbic acid, Mg*
Corn grits, degermed											
Unenriched Dry	362	8.7	.8	78.1	4	1.0	300[15]	.13	.04	1.2	(0)
Corn meal, white or yellow											
Degermed unenriched Dry	363	7.9	1.2	78.4	6	1.1	300[17]	.14	.05	1.0	(0)
Crabs, Atlantic and Pacific, hardshell											
Raw	86	16.1	1.6	.6	(39)	(.8)	—	.14	.06	2.7	—
Crackers											
Graham	393	8.0	10.0	74.3	20	1.9	(0)	.30	.12	1.5	(0)
Saltines	431	9.2	11.8	71.1	19	1.0	(0)	.06	.04	1.0	(0)
Soda, plain	420	9.6	9.6	72.7	20	1.1	(0)	.06	.05	1.1	(0)
Cranberries Raw	48	.4	.7	11.3	14	.6	40	(.03)	(.02)	.1	12
Cranberry sauce, sweetened, canned or cooked	198	.1	.3	51.4	(8)	(.3)	(40)	(.02)	(.02)	(.1)	2
Cream											
Light, table or coffee	204	2.9	20.0	4.0	97	.1	830	.03	.14	.1	1
Heavy or whipping	330	2.3	35.0	3.2	78	.0	1,440	.02	.11	.1	1
Cress, garden Raw	41	4.2	1.4	5.3	211	(2.9)	2,970	.11	.17	1.0	87
Cucumbers, raw	12	.7	.1	2.7	10	.3[18]	0[18]	.03	.04	.2	8
Currants red raw	55	1.2	.2	13.6	36	.9	120	.04	—	—	36
*Custard, baked	114	5.3	5.4	11.2	114	.5	340	.05	.28	.1	Trace
Dandelion greens Cooked	44	2.7	.7	8.8	187	3.1	15,170	.13	.12	7)	16
Dates, "fresh" and dried	284	2.2	.6	75.4	72	2.1	60	.09	.10	2.2	(0)
Doughnuts, cake type	425	6.6	21.0	52.7	73	(.7)	140	.16	.13	1.2	(0)
Eggplant, raw	24	1.1	.2	5.5	15	.4	30	.04	.05	.6	5
Eggs, hen, fresh, stored or frozen											
Raw											
Whole	162	12.8	11.5	.7	54	2.7	1,140	.10	.29	.1	0
White	50	10.8	.0	.8	6	.2	(0)	0	.26	(.1)	0
Yolk	361	16.3	31.9	.7	147	7.2	3,210	.27	.35	Trace	0
Cooked											
*Scrambled	171	11.0	12.8	2.2	81	2.1	1,040	.08	.27	.1	0
Poached	160	12.7	11.4	.6	54	2.7	1,130	.08	.24	.1	0
Endive, raw	20	1.6	.2	4.0	79	1.7	3,000	.07	.12	.4	11
Farina, unenriched, raw	370	10.9	.8	77.4	28	1.0	(0)	.06	.06	.8	(0)
Figs											
Raw	79	1.4	.4	19.6	54	.6	80	.06	.05	.5	2
Dried	270	4.0	1.2	68.4	186	3.0	80	.10	.12	1.7	(0)

Fig bars	350	4.2	4.8	75.8	69	1.3	0	.02	.06	0.9	(0)
Flounder, summer and winter, raw	68	14.9	.5	0	61	.8	—	.06	.05	1.7	—
Fruit cocktail canned, solids and liquid	70	.4	.2	18.6	9	.4	160	.01	.01	.4	2
Gelatin, dry											
Plain	335	85.6	.1	0	(0)	(0)	(0)	(0)	(0)	(0)	(0)
Dessert powder	350	9.4	0	88.7	(0)	(0)	(0)	(0)	(0)	(0)	(0)
*Gelatin dessert, ready-to-serve											
Plain	65	1.6	0	15.2	(0)	(0)	(0)	(0)	(0)	(0)	(0)
With fruit added	71	1.4	.1	17.5	6	.3	110	.03	.02	.2	3
**Gingerbread*	327	3.9	12.0	51.6	114	2.5	100	.04	.08	1.0	(0)
Grapefruit											
Raw	40	.5	.2	10.1	22	.2	Trace	.04	.02	.2	40
Canned in sirup, solids and liquid	72	.6	.2	19.1	13	.3	Trace	.03	.02	.2	30
Grapefruit juice											
Fresh	36	.5	.1	9.2	8	.3	Trace	.04	.02	.2	40
Canned											
Unsweetened	38	.5	.1	9.8	8	.3	Trace	.03	.02	.2	35
Sweetened	52	.5	.1	13.7	8	.3	Trace	.03	.02	.2	35
Grapefruit juice concentrate frozen	147	1.9	.4	38.1	31	1.2	30	.12	.07	.7	135
Grapefruit-orange juice blend											
Canned											
Unsweetened	40	.6	.1	10.4	9	.3	40	.05	.02	.2	38
Sweetened	52	.5	.1	13.9	9	.3	40	.05	.02	.2	38
Frozen concentrate	147	2.2	.4	37.9	33	1.1	160	.17	.06	.7	137
Grapes raw											
American type (slip skin) as Concord Delaware Niagara and Scuppernong	70	1.4	1.4	14.9	17	.6	80	.06	.04	.2	4
European type (adherent skin) as Malaga *Muscat Sultanina (Thompson* Seedless) and Flame Tokay	66	.8	.4	16.7	17	.6	80	.06	.04	.2	4
Grape juice bottled commercial	67	.4	0	18.2	10	.3	—	.04	.05	(.2)	Trace
Guavas common raw	70	1.0	.6	17.1	30	.7	250	.07	.04	1.2	302
Haddock											
Raw	79	18.2	.1	0	23	.7	–	.05	.08	2.4	—
Cooked fried	158	18.7	5.5	7.0	18	.6	–	.04	.09	2.6	—
Halibut											
Raw	126	18.6	5.2	0	13	0.7	410	.07	.06	9.2	—
Cooked broiled	182	26.2	7.8	0	14	.8	–	.06	.07	10.5	—
Herring Atlantic raw	191	18.3	12.5	0	–	1.1	110	.02	.15	3.4	—
Herring lake raw	140	18.5	6.8	0	12	.5	(100)	.09	.09	3.1	—

[16] Vitamin A based on yellow corn grits white corn grits contain only a trace
[17] Vitamin A based on yellow corn meal white corn meal contains only a trace
[18] Based on pared cucumbers unpared contain about 1.2 mg iron and 260 I U vitamin A per 100 gm

TABLE 144.—COMPOSITION OF FOODS, 100 GRAMS, EDIBLE PORTION *—(*Continued*)

Food and description	*Food energy, Cal*	*Protein, Gm*	*Fat, Gm*	*Carbohydrate Total, Gm*	*Calcium, Mg*	*Iron, Mg*	*Vitamin A value, I U*	*Thiamine, Mg*	*Riboflavin, Mg*	*Niacin, Mg*	*Ascorbic acid, Mg*
Herring, Pacific raw	91	16 6	2 6	0	—	—	100	02	22	(2 2)	—
Herring, smoked kippered	211	22 2	12 9	0	66	(1 4)	0	Trace	28	(2 9)	—
Honey, strained or extracted	294	3	0	79 5	5	9	(0)	Trace	04	2	4
Honeydew melon, raw	32	5	0	8 5	(17)	(4)	40	05	03	2	23
Ice cream, plain	207	4 0	12 5	20 6	123	1	520	04	19	1	1
Jams, marmalades preserves	278	5	3	70 8	12	3	10	02	02	2	6
Jellies	252	2	0	65 0	(12)	(3)	(10)	(02)	(02)	(2)	4
Kale, cooked	40	3 9	6	7 2	225	2 2	8,380	07	23	1 7	51
Kidneys, raw											
Beef	141	15 0	8 1	9	9	7 9	1,150	37	2 55	6 4	13
Kohlrabi, cooked	30	2 1	1	6 7	46	6	Trace	04	04	2	37
Lamb											
Retail items,[19] medium fat											
Rib chop, cooked	418	24	35	0	11	3 0	(0)	14	26	5 6	0
Shoulder roast (wholesale 3-rib), cooked	342	21	28	0	9	2 6	(0)	12	22	4 6	0
Leg roast (wholesale leg), cooked	274	24	19	0	10	3 1	(0)	14	25	5 1	0
Lard	902	0	100	0	0	0	0	0	0	0	0
Lemons	32	9	6	8 7	40	6	0	04	Trace	1	50
Lemon juice											
Fresh	24	0 4	0 2	7 7	14	0 1	0	04	Trace	1	50
Canned											
Unsweetened	24	4	2	7 7	14	1	0	04	Trace	1	42
Concentrate	116	2 0	1 0	37 5	68	5	(0)	22	02	7	230
Lentils dry											
Whole (entire seeds)	337	25 0	1 0	59 5	59	7 4	570	56	24	2 2	5
Lettuce, raw											
Headed	15	1 2	2	2 9	22	5	540	04	08	2	8
All other	15	1 2	2	2 9	62	1 1	1,620	04	08	2	18
Limes	37	8	1	12 3	(40)	(6)	0	(04)	(Trace)	(1)	27
Lime juice, fresh	24	4	0	8 3	(14)	(1)	0	(04)	(Trace)	(1)	27
Liver											
Beef											
Cooked, fried	208	23 0	7 7	9 7	8	7 8	53,500	26	3 96	14 8	31
Lobster											
Raw	88	16 2	1 9	5	61	6	—	(13)	06	(1 9)	—
Canned	92	18 4	1 3	4	65	8	—	(03)	07	(2 2)	—

Loganberries, raw	62	1.0	.6	15.0	35	1.2	(200)	(.03)	(.07)	(.3)	24
Macaroni, Unenriched											
Dry	377	12.8	1.4	76.5	22	1.5	(0)	.09	.06	2.0	(0)
*Cooked	149	5.1	.6	30.2	9	.6	(0)	.02	.02	.5	(0)
*Macaroni and cheese, baked	211	8.1	11.0	19.7	191	.5[21]	450	.03[21]	.10[21]	.4[21]	Trace
Mackerel											
Raw, common Atlantic	158	18.7	12	0	5	1.0	(450)	.15	.35	8.4	—
Mangos raw	66	.7	.2	17.2	9	.2	6,350	.06	.06	.9	41
Margarine	720	.6	81	.4	20	0	3,300[22]	(0)	(0)	(0)	(0)
Milk cow											
Fluid (pasteurized and raw)											
Whole	68	3.5	3.9	4.9	118	.1	(160)	.04	.17	.1	1
Nonfat (skim)	36	3.5	.1	5.1	123	.1	Trace	.04	.18	.1	1
Canned											
Evaporated (unsweetened)	138	7.0	7.9	9.9	243	.2	400	.05	.36	.2	1
Condensed (sweetened)	320	8.1	8.4	54.8	273	.2	(430)	.05	.39	.2	1
Dried											
Whole	492	25.8	26.7	38.0	949	.6	1,400	.30	1.46	.7	6
Nonfat solids (skim)	362	35.6	1.0	52.0	1,300	.6	(40)	.35	1.96	1.1	7
Malted [23]											
Dry powder	407	14.6	8.5	70.7	287	2.1	1,020	.33	.54	—	(0)
*Beverage	104	4.6	4.4	11.8	135	.3	250	.07	.21	—	1
*Chocolate flavored	74	3.2	2.2	10.6	109	.1	90	.03	.16	.1	1
Milk goat fluid	67	3.3	4.0	4.6	129	.1	(160)	.04	.11	.3	1
Molasses cane											
Second extraction or medium	232	—	—	60[24]	290	6.0	—	—	.12	1.2	—
*Muffins made with											
Enriched flour	280	8.0	8.4	42.1	206	1.6	100	.18	.21	1.5	(0)
Mung bean sprouts raw	23	2.9	.2	4.1	29	.8	10	.07	.09	.5	15
Mushrooms											
Canned, solids and liquid	11	1.4	.2	3.7	(7)	(.8)	0	.02	.25	2.0	—
Mustard greens cooked	22	2.3	.3	4.0	220	2.9	7,180	.06	.18	.7	45
Noodles (containing egg)											
Unenriched											
Dry	381	12.6	3.4	73.2	22	2.1	200	.20	.11	2.7	(0)
*Cooked	67	2.2	.6	12.8	4	.4	30	.03	.02	.4	(0)

[20] Values for raw items are from the medium fat wholesale cuts considered to be nearest approximations for indicated retail items

[21] If enriched macaroni is used in the recipe, the values for iron, thiamine, riboflavin and niacin would be 0.7 mg, 0.10 mg / 0.20 mg / and 0.9 mg, respectively

[22] Based on the average vitamin A content of fortified margarine. Most of the margarines manufactured for use in the United States have 15,000 I.U. of vitamin A added per pound. The minimum Federal specifications for fortified margarine require the addition of 9,000 I.U. of vitamin A per pound

[23] Based on unfortified products

[24] Total sugars

TABLE 144 —COMPOSITION OF FOODS, 100 GRAMS, EDIBLE PORTION *—(Continued)

Food and description	Food energy, Cal	Protein, Gm	Fat, Gm	Carbohydrate Total, Gm	Calcium, Mg	Iron, Mg	Vitamin A value, I U.	Thiamine, Mg	Riboflavin, Mg	Niacin, Mg	Ascorbic acid, Mg
Herring, Pacific, raw	94	16 6	2 6	0	—	—	100	02	22	(2 2)	—
Herring, smoked, kippered	211	22 2	12 9	0	60	(1 4)	0	Trace	28	(2 9)	—
Honey, strained or extracted	294	3	0	79 5	5	9	(0)	Trace	04	2	4
Honeydew melon raw	32	5	0	8 5	(17)	(4)	40	05	03	2	23
Ice cream, plain	207	4 0	12 5	20 6	123	1	520	04	19	1	1
Jams, marmalades, preserves	278	5	3	70 8	12	3	10	02	02	2	6
Jellies	252	2	0	65 0	(12)	(3)	(10)	(02)	(02)	(2)	4
Kale cooked	40	3 9	6	7 2	225	2 2	8,380	07	23	1 7	51
Kidneys, raw											
Beef	141	15 0	8 1	9	9	7 9	1,150	37	2 55	6 4	13
Kohlrabi cooked	30	2 1	1	6 7	46	6	Trace	04	04	2	37
Lamb											
Retail items [19] medium fat											
Rib chop cooked	418	24	35	0	11	3 0	(0)	14	26	5 6	0
Shoulder roast (wholesale 3-rib), cooked	342	21	28	0	9	2 6	(0)	12	22	4 6	0
Leg roast (wholesale leg), cooked	274	24	19	0	10	3 1	(0)	14	25	5 1	0
Lard	902	0	100	0	0	0	0	0	0	0	0
Lemons	32	9	6	8 7	40	6	0	04	Trace	1	50
Lemon juice											
Fresh	24	0 4	0 2	7 7	14	0 1	0	04	Trace	1	50
Canned											
Unsweetened	24	4	2	7 7	14	1	0	04	Trace	1	42
Concentrate	116	2 0	1 0	37 5	68	5	(0)	22	02	7	230
Lentils, dry											
Whole (entire seeds)	337	25 0	1 0	59 5	59	7 4	570	56	24	2 2	5
Lettuce raw											
Headed	15	1 2	2	2 9	22	5	540	04	08	2	8
All other	15	1 2	2	2 9	62	1 1	1,620	04	08	2	18
Limes	37	8	1	12 3	(40)	(6)	0	(04)	(Trace)	(1)	27
Lime juice, fresh	24	4	0	8 3	(14)	(1)	0	(04)	(Trace)	(1)	27
Liver											
Beef											
Cooked, fried	208	23 6	7 7	9 7	8	7 8	53 500	26	3 96	14 8	31
Lobster											
Raw	88	16 2	1 9	5	61	6	—	(13)	06	(1 9)	—
Canned	92	18 4	1 3	4	65	8	—	(03)	07	(2 2)	—

Loganberries raw	62	1 0	6	15 0	35	1 2	(200)	(03)	(07)	(3)	24
Macaroni Unenriched											
Dry	377	12 8	1 4	76 5	22	1 5	(0)	09	06	2 0	(0)
*Cooked	149	5 1	6	30 2	9	6	(0)	02	02	5	(0)
*Macaroni and cheese baked	211	8 1	11 0	19 7	191	5[31]	450	03[31]	10[31]	4[31]	Trace
Mackerel											
Raw common Atlantic	188	18 7	12	0	5	1 0	(450)	15	35	8 4	—
Mangos raw	66	7	2	17 2	9	2	6,350	06	06	9	41
Margarine	720	6	81	4	20	0	3,300[32]	(0)	(0)	(0)	(0)
Milk cow											
Fluid (pasteurized and raw)											
Whole	68	3 5	3 9	4 9	118	1	(160)	04	17	1	1
Nonfat (skim)	36	3 5	1	5 1	123	1	Trace	04	18	1	1
Canned											
Evaporated (unsweetened)	138	7 0	7 9	9 9	243	2	400	05	36	2	1
Condensed (sweetened)	320	8 1	9 4	54 8	273	2	(430)	05	39	2	1
Dried											
Whole	492	25 8	26 7	38 0	949	6	1,400	30	1 46	7	6
Nonfat solids (skim)	362	35 6	1 0	52 0	1,300	6	(40)	35	1 96	1 1	7
Malted[33]											
Dry powder	407	14 6	8 5	70 7	287	2 1	1,020	33	54	—	(0)
*Beverage	104	4 6	4 4	11 8	135	3	250	07	21	—	1
*Chocolate flavored	74	3 2	2 2	10 6	109	1	90	03	16	1	1
Milk, goat fluid	67	3 3	4 0	4 6	129	1	(160)	04	11	3	1
Molasses cane											
Second extraction or medium	232	—	—	60[34]	290	6 0	—	—	12	1 2	—
*Muffins, made with											
Enriched flour	280	8 0	8 4	42 1	206	1 6	100	18	21	1 5	(0)
Mung bean sprouts raw	23	2 9	2	4 1	29	8	10	07	09	5	15
Mushrooms											
Canned, solids and liquid	11	1 4	2	3 7	(7)	(8)	0	02	25	2 0	—
Mustard greens cooked	22	2 3	3	4 0	220	2 9	7 180	06	18	7	45
Noodles (containing egg)											
Unenriched											
Dry	381	12 6	9 4	73 3	22	2 1	200	20	11	2 3	(0)
*Cooked	67	2 2	6	12 8	4	4	30	03	02	4	(0)

[30] Values for raw items are from the medium fat wholesale cuts considered to be nearest approximations for indicated retail items

[31] If enriched macaroni is used in the recipe the values for iron, thiamine riboflavin, and niacin would be 0 7 mg , 0 10 mg / 0 20 mg / and 0 9 mg , respectively

[32] Based on the average vitamin A content of fortified margarine Most of the margarines manufactured for use in the United States have 15,000 I U of vitamin A added per pound The minimum Federal specifications for fortified margarine require the addition of 9,000 I U of vitamin A per pound

[33] Based on unfortified products

[34] Total sugars

TABLE 144 — COMPOSITION OF FOODS, 100 GRAMS, EDIBLE PORTION * — (*Continued*)

Food and description	*Food energy, Cal*	*Protein Gm*	*Fat, Gm*	*Carbohydrate Total, Gm*	*Calcium, Mg*	*Iron, Mg*	*Vitamin A value, I U*	*Thiamine, Mg*	*Riboflavin, Mg*	*Niacin, Mg*	*Ascorbic acid, Mg.*
Oatmeal or rolled oats											
Dry	390	14.2	7.4	68.2	53	4.5	(0)	60	14	1.0	(0)
*Cooked	63	2.3	1.2	11.0	9	7	(0)	10	02	2	(0)
Oils, salad or cooking	884	0	100	0	0	0	0	0	0	0	0
Okra, cooked	32	1.8	2	7.4	82	7	740	06	06	8	20
Olives pickled											
Green	132	1.5	13.5	4.0	87	1.6	300	Trace	—	—	—
Ripe											
Mission	191	1.8	21.0	2.6	87	1.6	60	Trace	Trace	—	—
Other varieties (as ascalano manzanilla, and sevilano)	128	1.2	13.5	3.1	87	1.6	60	Trace	Trace	—	—
Onions mature											
Raw	45	1.4	0.2	10.3	32	5	50	03	04	2	9
Cooked	38	1.0	2	8.7	32	5	50	02	03	2	6
Onions, young green	45	1.0	2	10.6	135	9	(50)	(03)	(04)	(2)	24
Oranges	45	9	2	11.2	33	4	(190)	08	03	2	49
Orange juice											
Fresh	44	8	2	11.0	19	2	(190)	08	03	2	49
Canned											
Unsweetened	44	8	2	11.1	10	3	(100)	07	02	2	42
Sweetened	54	6	2	13.9	10	3	(100)	07	02	2	42
range juice concentrate											
Canned	229	4.2	7	58.0	61	1.6	(510)	37	08	1.1	221
Frozen	149	2.7	7	37.1	34	1.0	(330)	24	05	7	141
ysters, meat only, raw	84	9.8	2.1	5.6	94	5.6	320	15	20	1.2	—
Oyster stew											
1 part oysters to 3 parts milk by volume	91	5.3	5.4	5.3	117	1.5	280	06	18	4	—
Pancakes (griddlecakes), baked											
Wheat (home recipe)											
With unenriched flour	218	6.8	9.2	26.6	158	6	200	06	13	3	Trace
Buckwheat, with buckwheat pancake mix	170	6.1	8.4	20.9	249	1.2	110	16	16	9	Trace
apayas raw	39	6	1	10.0	20	3	1,750	03	04	3	56
arsley common raw	50	3.7	1.0	9.0	193[a]	4.3	8,230	11	28	1.4	193
arsnips, cooked	60	1.0	5	13.9	57	7	0	06	10	2	12
eaches											
Raw	46	5	1	12.0	8	6	880	02	05	9	8

Canned, solids and liquid											
Water pack	27	.5	.1	6.8	5	.4	450	.01	.02	.7	4
Frozen	78	.4	.1	20.2	6	.4	520	.01	.03	.5	4
Dried, sulfured											
Uncooked	265	3.0	.6	69.4	44	6.9	3,250	.01	.20	5.4	19
Peanuts, Virginia type, roasted, shelled	559	26.9	44.2	23.6	74	1.9	0	.30	.13	16.2	(0)
Peanut butter	576	26.1	47.8	21.0	74	1.9	0	.12	.13	16.2	(0)
Pears											
Raw	63	.7	.4	15.8	13	.3	20	.02	.04	.1	4
Canned, solids and liquid											
Water pack	31	.3	.1	8.2	8	.2	Trace	.01	.02	.1	2
Peas, green immature											
Cooked	70	4.9	.4	12.1	22	1.9	720	.25	.14	2.3	15
Canned, solids and liquid	68	3.4	.4	12.9	25	1.8	540	.11	.06	1.0	8
Frozen	75	5.7	.3	12.9	17	1.5	670	.33	.11	1.9	18
Peas, mature dry seeds											
Split, without seed coat	344	24.5	1.0	61.7	33	5.1	370	.77	.28	3.1	2
Pecans	696	9.4	73.0	13.0	74	2.4	50	.72	.11	.9	2
Peppers, green raw	25	1.2	.2	5.7	11	.4	630	.04	.07	.4	120
Cooked parboiled then baked	26	1.3	.2	6.0	11	.4	740	.04	.07	.4	99
Persimmons, Japanese or Kaki, raw	78	.8	.4	20.0	6	.3	2,710	.05	.05	Trace	11
Pickles											
Dill, cucumber	11	.7	.2	2.1	25	1.2	310	Trace	.06	Trace	6
Fresh, cucumber (as bread and butter pickles)	70	.9	.2	17.0	32	1.8	180	.02	.04	Trace	9
Sour, cucumber or mixed	11	.5	.2	2.2	25	1.2	310	Trace	.06	Trace	6
Sweet, cucumber or mixed	108	.8	.4	26.4	16	1.3	110	(0)	.02	Trace	7
Pies											
*Apple	246	2.1	9.5	39.5	7	.4	160	.03	.02	.2	1
*Blueberry	216	2.1	6.9	37.5	10	.5	120	.02	.03	.2	4
*Cherry	253	2.4	9.8	40.4	10	.4	380	.03	.02	.2	1
Custard	204	5.2	8.7	26.3	125	1.2	230	.05	.16	.3	(0)
Lemon meringue	252	3.6	10.1	37.4	20	.5	170	.03	.08	.2	1
Mince[74]	252	2.5	6.9	45.6	16	2.2	10	.07	.04	.4	1
*Pumpkin	202	4.2	9.6	25.8	54	.8	1,010	.03	.12	.3	(0)
Pineapple											
Raw	52	.4	.2	13.7	16	.3	130	.08	.02	.2	24
Canned, sirup pack, solids and liquid	78	.4	.1	21.1	29	.6	80	.07	.02	.2	9
Pineapple juice, canned	49	.3	.1	13.0	15	.5	80	.05	.02	.2	9
Plantain or baking banana, raw	119	1.1	.4	31.2	7	.7	[75]	.06	.04	.6	14

[74] The proximate constituents, calcium, phosphorus, and vitamin A are calculated from a recipe.
[75] The vitamin A values range from about 10 I U per 100 gm of white fleshed plantains to 1,200 I U per 100 gm of deeper yellow fleshed varieties

TABLE 144 —COMPOSITION OF FOODS, 100 GRAMS, EDIBLE PORTION *—(*Continued*).

Food and description	*Food energy, Cal*	*Protein, Gm*	*Fat, Gm*	*Carbohydrate Total, Gm.*	*Calcium, Mg*	*Iron, Mg*	*Vitamin A value, I.U.*	*Thiamine, Mg*	*Riboflavin, Mg*	*Niacin, Mg*	*Ascorbic acid, Mg*
Plums (all, excluding prunes) raw	50	7	2	12 9	17	5	350	06	04	5	5
Plums (Italian prunes) canned											
Sirup pack, solids and liquid (except pits)	76	4	1	20 4	8	1 1	230	03	03	4	1
Popcorn, popped	386	12 7	5 0	76 7	(11)	(2 7)	(0)	(39)	(12)	(2 2)	(0)
Pork, fresh											
Retail items [17] medium fat											
Ham, cooked	400	24	33	0	11	3 1	(0)	53	24	4 7	0
Loin or chops, cooked	333	23	26	0	11	3 0	(0)	83	24	5 0	0
Pork, cured											
Ham, smoked[18] medium fat											
Cooked	397	23	33	(4)	10	2 9	(0)	54	21	4 2	0
Luncheon meat canned, spiced	289	14 9	24 3	1 5	9	2 2	(0)	32	22	2 8	0
Potatoes											
Cooked											
Baked	98	2 4	1	22 5	13	8	20	11	05	1 4	17
Boiled, peeled before cooking	83	2 0	1	19 1	11	7	20	09	03	1 0	14
**French-fried*	393	5 4	*19 1*	*52 0*	30	*1 9*	*50*	18	11	3 3	28
*Hash-browned after holding overnight	241	3 3	11 7	31 9	18	1 2	30	08	06	1 7	7
*Mashed milk added	81	2 2	7	17 0	27	6	40	08	05	9	7
Potato chips	544	6 7	37 1	49 1	(30)	(1 9)	(50)	(18)	(11)	(3 2)	11
Pretzels	369	8 8	3 2	74 5	(12)	(7)	(0)	(01)	(04)	(7)	(0)
Prunes, dried, unsulfured											
Uncooked	268	2 3	6	71 0	54	3 9	1,890	10	16	1 7	3
*Cooked, no sugar added	125	1 1	3	33 0	25	1 8	890	03	08	8	1
Prune juice canned	71	4	0	19 3	(25)	(1 8)	—	(03)	(08)	4	(1)
Pumpkin, canned	33	1 0	3	7 9	(20)	(7)	3,400	02	06	5	—
Raw	31	1 2	2	7 3	21	8	(3,400)	(05)	(08)	(6)	8
Radishes, raw	20	1 2	1	4 2	37	1 0	30	03	02	3	24
Raisins, unsulfured											
Dried	268	2 3	5	71 2	78	3 3	50	15	08	5	Trace
Raspberries											
Black, raw	74	1 5	1 6	15 7	40	9	0	02	(07)	(3)	(24)
Red											
Raw	57	1 2	4	13 8	40	9	130	02	(07)	(3)	24
Frozen	98	8	3	24 7	28	6	80	01	(04)	(2)	16

Rhubarb stems only											
Raw	16	5	1	3 8	51[29]	5	30	01	—	1	9
Rice											
Brown raw	360	7 5	1 7	77 7	39	2 0	(0)	32	05	4 6	(0)
White or milled											
Raw	362	7 6	3	79 4	24	8	(0)	07	03	1 6	(0)
*Cooked	119	2 5	1	26 2	8	3	(0)	01	01	4	(0)
Rice products											
Puffed	392	5 9	6	87 7	21	1 8	(0)	08	08	9	(0)
*Rolls											
Plain, enriched (pan rolls)	309	9 0	5 5	55 1	55	1 8[30]	0	24[30]	15[30]	2 2[30]	(0)
Rutabagas, cooked	32	8	1	7 5	55	4	350	05	07	7	21
Rye flour dark	318	16 3	2 6	68 1	54	4 5	(0)	61	22	2 7	(0)
Rye wafers or Swedish health bread '	324	12 4	1 2	75 3	50	4 4	(0)	32	20	1 2	(0)
Salad dressings											
Commercial, plain (Mayonnaise type)[31]	384	1 1	36 8	13 9	9	4	140	02	03	(0)	0
French	394	6	35 5	20 3	(0)	(0)	(0)	(0)	(0)	(0)	(0)
Mayonnaise[31]	708	1 5	78	3 0	19	1 0	210	04	04	(0)	0
Salmon											
Raw, Pacific (Chinook or King)	223	17 4	16 5	0	—	(9)	310	10	23	7 2	9
Canned solids and liquid (incl bones) average	165	20 6	8 5	0	216	9	134	03	16	7 4	
Sardines											
Atlantic type, canned *in oil*											
Drained solids	214	25 7	11 0	1 2	386	2 7	220	02	17	4 8	(0)
Sauerkraut canned											
Drained solids	22	1 4	3	4 4	36	(5)	40	03	06	1	16
Sausage											
Bologna	221	14 8	15 9	3 6	(9)	2 2	(0)	18	19	2 7	0
Frankfurter, cooked	248	14	20	2	6	1 2	(0)	16	18	2 5	0
Liver, liverwurst	263	16 7	20 6	1 5	9	5 4	5 750	17	1 12	4 6	(0)
Pork, links or bulk, raw	450	10 8	44 8	0	6	1 6	(0)	43	17	2 3	0
Scallops, raw (edible muscle)	78	14 8	1	3 4	26	1 8	0	(04)	10	1 4	—
Shad or American shad, raw	168	18 7	9 8	0	—	5	—	(15)	24	(8 4)	—
*Sherbet	123	1 5	0	30 0	50	0	0	02	08	Trace	(0)

[27] Values for raw items are *from medium* fat wholesale cuts considered to be nearest approximations for indicated *retail items*

[28] Values for raw items are from the medium fat wholesale cuts considered to be *nearest approximations* for indicated retail items

[29] Calcium may not be available because *of presence of oxalic* acid

[30] Iron, thiamine, *riboflavin*, and niacin are based on the minimum level of enrichment specified in the standard*s of identity* of breads proposed by the Federal Security Agency and published in the Federal Register, August *3, 1943*

[31] Minerals and vitamins are calculated *from a recipe*

TABLE 144 —COMPOSITION OF FOODS, 100 GRAMS, EDIBLE PORTION *—(*Continued*).

Food and description	*Food energy, Cal*	*Protein, Gm*	*Fat, Gm*	*Carbohydrate Total, Gm*	*Calcium, Mg*	*Iron, Mg*	*Vitamin A value, I U*	*Thiamine, Mg*	*Riboflavin, Mg*	*Niacin, Mg.*	*Ascorbic acid, Mg*
Shrimp, canned											
Dry pack or drained solids of wet pack	127	26 8	1 4	—	115	3 1	60	01	03	2 2	(0)
Sirup, table blends (chiefly corn sirup)	286	(0)	(0)	(74)	46	4 1	0	0	01	1	(0)
Soups canned [22]											
Bean, ready-to-serve	76	3 4	2 0	11 8	38	1 1	—	04	04	3	—
Beef, ready-to-serve	40	2 4	1 4	4 4	6	2	—	—	—	—	—
Bouillon, broth and consomme											
Ready-to serve	4	(1)	—	(0)	1	4	0	0	02	3	0
Chicken, ready-to-serve	30	1 4	1 0	3 8	8	2	—	01	05	6	—
Clam chowder, ready-to-serve	34	1 8	9	4 9	14	1 4	—	—	—	—	—
Cream soup (asparagus, celery or mushroom), ready-to-serve	79	2 8	4 6	7 2	85	2	80	02	08	Trace	(0)
Pea, ready-to-serve	57	2 6	8	10 2	13	6	(180)	07	03	5	2
Tomato, ready-to-serve	37	9	9	7 3	10	4	(500)	01	04	3	4
Vegetable, ready-to-serve	33	1 7	7	5 8	13	3	—	02	03	4	3
Soybeans, whole, mature, dried	331	34 9	18 1	34 8[23]	227	8 0	110	1 07	31	2 3	Trace
Soybean flour, flakes, grits											
Medium fat	264	42 5	6 5	37 2[23]	244	13 0	110	82	34	2 6	(0)
Spaghetti, unenriched											
Dry	377	12 8	1 4	76 5	22	1 5	(0)	09	06	2 0	(0)
*Cooked	149	5 1	6	30 2	9	6	(0)	02	02	5	(0)
Spinach											
Raw	20	2 3	3	3 2	81[24]	3 0	9,420	11	20	6	59
Cooked	26	3 1	6	3 6	124[24]	2 0	11,780	08	20	6	30
Squash, summer											
Cooked, diced	16	6	1	3 9	15	4	200	04	07	6	11
Squash, winter											
Cooked, boiled, mashed	38	1 5	3	8 8	19	6	4,950	04	10	.4	5
Starch, pure (including arrowroot, corn, etc)	362	5	2	87	(0)	(0)	(0)	(0)	(0)	(0)	(0)
Strawberries											
Raw	37	8	5	8 3	28	8	60	03	07	3	60
Frozen	106	6	4	26 6	22	6	40	02	05	2	41
Sugars											
Granulated, cane or beet	385	(0)	(0)	99 5	—	—	(0)	(0)	(0)	(0)	(0)
Powdered	385	(0)	(0)	99 5	—	—	(0)	(0)	(0)	(0)	(0)

Brown	370	(0)	(0)	95 5	76[35]	2 6	(0)	(0)	(0)	(0)	(0)
Maple	348	—	—	(90)	—	—	—	—	—	—	—
Sweet potatoes[36]											
Cooked											
Baked	152	2 2	9	34 4	37	9	9,510	10	06	8	23
Boiled	123	1 8	7	27 9	30	7	7,700	09	05	6	20
Swordfish, Cooked, broiled	178	27 4	6 8	0	20	1 1	2,300	05	08	10 3	(0)
Tangerines (including other Mandarin type oranges)	44	8	3	10 9	(33)	(4)	(420)	07	(03)	(2)	31
Tapioca, dry	360	6	2	86 4	12	(1 0)	(0)	(0)	(0)	(0)	(0)
Tomatoes											
Raw	20	1 0	3	4 0	11	6	1,100	06	04	5	23
Canned or cooked	19	1 0	2	3 9	(11)	(6)	1,050	06	03	7	16
Tomato juice, canned	21	1 0	2	4 3	(7)	(4)	1,050	05	03	8	16
Tomato catsup	98	2 0	4	24 5	12	8	(1,880)	09	07	2 2	11
Tomato purée, canned	36	1 8	5	7 2	(11)	(1 1)	1,880	09	07	1 8	28
Tongue, beef, medium fat, raw	207	18 4	15	4	9	2 8	(0)	12	29	5 0	(0)
Tuna fish, canned											
Drained solids	198	29 0	8 2	0	(8)	1 4	80	05	12	12 8	(0)
Turkey, medium fat, raw	268	20 1	20 2	0	23	3 8	Trace	09	14	8 0	(0)
Turnips, cooked	27	8	2	6 0	40	5	Trace	04	06	4	18
Turnip greens											
Cooked Boiled in small amount of water until tender	30	2 9	4	5 4	259	2 4	10 600	06	41	7	60
Veal											
Carcass or side excluding kidney fat, raw Medium fat	190	19 1	12	0	11	2 9	(0)	14	25	6 4	0
Retail items[37] medium fat											
Cutlet, boned (wholesale round)											
Cooked	219	28	11	0	12	3 5	(0)	08[38]	28[38]	6 1[38]	0
Shoulder roast boned (wholesale chuck)											
Cooked	228	28	12	0	12	3 6	(0)	13	31	7 9	0

[32] All the ready-to-serve soups are calculated from equal weights of the condensed soup and water except cream soup which was based on equal weights of the condensed soup and milk

[33] Approximately 40 per cent of this total amount of carbohydrate calculated by difference is sugar, starch, and dextrin The remaining portion is made up of materials thought to be utilized only poorly, if at all, by the body

[34] Calcium may not be available because of presence of oxalic acid

[35] Calcium and phosphorus are based on dark brown sugar, values would be lower for light brown sugar

[36] If very pale varieties only were used, the vitamin A value would be very much lower

[37] Values for raw items are from the medium fat wholesale cuts considered to be nearest approximations for indicated retail items

[38] Data assume cut to be prepared by braising or pot roasting Use of proportionate quantity of drippings would add approximately 50 per cent more thiamine and niacin and 25 per cent more riboflavin

TABLE 44.—COMPOSITION OF FOODS, 100 GRAMS, EDIBLE PORTION *—*Continued*.

Food and description	*Food energy, Cal.*	*Protein, Gm.*	*Fat, Gm.*	*Carbohydrate, Total, Gm.*	*Calcium, Mg.*	*Iron, Mg.*	*Vitamin A value, I.U.*	*Thiamine, Mg.*	*Riboflavin, Mg.*	*Niacin, Mg.*	*Ascorbic acid, Mg.*
Vegetables, mixed, strained, canned, infant food	29	1.6	.1	6.9	30	1.0	[illegible]	.03	.03	.4	3
Vinegar	12	0	—	5.0	7	.5	—	—	—	—	—
*Waffles, baked											
With unenriched flour	287	9.3	10.6	37.5	192	1.0	370	.06	.15	.4	0
Walnuts, Persian or English	654	15.0	64.4	15.6	83	2.1	30	.48	.13	1.2	3
Watermelons	28	.5	.2	6.9	7	.2	590	.05	.05	.2	6
Wheat flours											
Whole, from hard wheats	333	13.3	2.0	71.0	41	3.3	0	.55	.12	4.3	0
Patent											
General-purpose or family flour											
Unenriched	364	10.3	1.0	76.1	16	.5	0	.06	.05	.9	0
Enriched	364	10.5	1.0	76.1	16	2.9*	0	.44*	.26*	3.5*	0
Bread flour											
Unenriched	365	11.8	1.1	74.7	16	.9	0	.08	.06	1.0	0
Cake or pastry flour	364	7.5	.8	79.4	17	.5	0	.03	.03	.7	0
Wheat products											
Flakes	355	10.8	1.6	80.2	45	3.0	[illegible]	.08	.15	4.5	0
Flakes (added iron, thiamine, and niacin)	355	10.8	1.6	80.2	45	4.2	0	.56	.15	5.4	0
Germ	361	25.2	10.0	49.5	84	8.1	0	2.05	.80	4.6	0
Puffed	355	10.8	1.6	80.2	45	3.0	0	.08	.15	4.5	0
Puffed (added iron, thiamine, and niacin)	355	10.8	1.6	80.2	45	4.2	0	.56	.15	5.4	0
Shredded, plain	360	10.1	2.5	80.1	47	3.5	0	.22	.12	4.4	0
Whey, fluid	26	.9	.3	5.1	51	.1	10	.04	.13	.1	—
Yeast											
Compressed, baker's	86	12.6	.4	12.0	25	4.9	0	.45	2.07	28.2	0
Dried, brewer's	273	36.9	1.6	37.4	106	18.2	0	9.69	5.45	35.2	0

* Vitamin A values range from 970 to 3,340 I.U. per 100 gm.

* Iron, thiamine, riboflavin, and niacin are based on the minimum level of enrichment specified in the standards of identity promulgated under the Food, Drug, and Cosmetic Act.

TABLE 145.—SUGAR CONTENT OF FOODSTUFFS

(From the *Sugar Research Foundation, Incorporated*, December 26, 1957.)

Fruit	*Total Sugars Per cent*	*Glucose Per cent*	*Fructose Per cent*	*Sucrose Per cent*	*References*
Apple					
Empire Eating		2.2	7.3	2.7	1
English Eating		1.7	6.1	3.6	2
English Cooking		1.8	5.0	2.4	
George Washington	12.7			3.5	3
Northern Spy	14.0			2.6	
Rome Beauty	6.3	1.1	4.5	0.6	4
Apricot					
Fresh		2.0	0.4	4.4	1,2
Dried		17.0	7.4	19.0	1
Banana					
fresh, very green	1.8			1.2	3
medium ripe	15.4			12.5	3
very ripe	18.2			11.1	3
fresh		5.8	3.8	6.6	1
fresh, more yellow than green as is	11.6	2.2	1.5	8.0	
more yellow than green on solids	44.8	8.6	5.6	30.6	
yellow, green tip as is	16,2	3.1	2.5	10.6	
yellow *on solids*	62.1	11.8	9.6	40.7	5
full yellow as is	18.7	4.0	2.8	12.0	
full on solids	74.4	15.8	10.9	47.6	
yellow flecked with brown as is	19.5	4.2	3.2	12.1	
yellow on solids	81.0	17.5	13.4	50.1	
Blackberries, fresh		3.2	2.9	0.2	1,2
Cherries					
fresh eating		4.7	7.2	0.0	1,2,6
fresh cooking		5.5	6.1	0.0	
Cranberries, fresh		2.7	0.7	0.1	1,2
Currants					
black fresh		2.4	3.7	0.6	
red fresh		2.3	1.9	0.2	1,2,6
white fresh		3.0	2.6	0.0	
Damsons, fresh		5.2	3.4	1.0	1,2,6
Figs					
fresh, green		5.5	4.0	0.0	1,6
dried		27.3	24.6	1.0	1,2,6
Gooseberries					
fresh, green		1.5	1.7	0.3	1,2
ripe		4.4	4.1	0.7	
Grapefruit,					
fresh	8.6			1.4	3
Fresh Cuban	9.0			3.7	
Grapes					
fresh Malaga	2.6			0.3	3
black		8.2	7.3	0.0	1,2
white		8.1	8.0	0.0	
Greengage, fresh		5.0	2.6	4.2	2
Lemons					
fresh whole	2.0			0.6	3
fresh whole		1.4	1.4	0.4	1,6
fresh juice	1.4			0.5	3
fresh juice		0.5	0.9	0.2	1,6

TABLE 145.—SUGAR CONTENT OF FOODSTUFFS—(*Continued*)
(From the *Sugar Research Foundation, Incorporated*, December 26, 1957.)

Fruit	*Total Sugars Per cent*	*Glucose Per cent*	*Fructose Per cent*	*Sucrose Per cent*	*References*
Loganberries, fresh whole		1.9	1.3	0.2	1,2
Melons					
fresh canteloupe		1.2	0.8	3.3	1,2
yellow		2.1	1.5	1.4	
Mulberries, fresh, whole		4.4	3.6	0.0	1,2,6
Orange					
fresh, whole Florida	9.6			4.6	
fresh, whole	*9.9*			*5.7*	3
fresh, whole California	*14.2*			*8.1*	
fresh, whole		2.5	1.8	4.2	1,2,6
fresh, juice	6.8			4.1	3
fresh, juice		2.4	2.4	4.7	1,2,6
Pears					
fresh, winter	11.9			1.7	3
fresh	10.5				7
fresh, whole	10.3				7
Empire English Eating		3.5	6.3	1.0	
English Cooking		2.4	7.0	0.3	1,2
English Cooking		2.2	6.0	1.1	
Peaches					
fresh		1.5	0.9	6.7	1,2,6
dried		13.2	10.0	29.8	2
Pineapple, fresh		2.3	1.4	7.9	1,2,6
Plums					
Fresh, Victoria Stone Free ripe	7.4				
Red Miscell, Stone Free, ripe	7.6				8
Green Golden Stone Free, ripe	5.7				
Green Golden	7.8				7
fresh, Victoria		4.0	1.3	4.3	1,2,6
cooking		3.5	1.3	1.5	
Pomegranate, fresh juice		5.5	6.1	0.0	1,2
Prunes, dry (17% waste)		25.4	11.8	2.6	1,2
Raspberries					
fresh ripe	3.6				8
fresh ripe	4.8				7
whole fruit		2.3	2.4	1.0	1,2,6
Strawberries					
fresh, med. ripe	4.1			0.3	3
fresh, ripe	5.5				8
fresh, ripe		2.6	2.3	1.3	1,2,6
fresh	5.4				
Tangerine	13.7			8.9	3
Dried Fruits					
Apricots		17.0	7.4	19.0	
Currants		33.2	26.2	3.7	
Dates (14% waste)		32.0	23.7	8.2	
Figs		27.3	21.6	1.0	1,2,6
Peaches		13.2	10.0	29.8	
Prunes (17% waste)		25.9	11.8	2.6	
Raisins (8% waste)		32.9	28.3	3.2	
Sultanas		32.9	28.1	3.7	

References

Table 146.—Per cent[a] of Sugars Found in Plant Material[*]

	Lead Clarification[b]			Ion-exchange Resin Clarification[c]		
Material	Sugars[d] Reducing	Total	Fructose Official[e]	Sugars[d] Reducing	Total	Fructose Official[e]
Cabbage	3 26	3 37	1 46	3 20	3 46	1 51
Carrots	2 30	4 90	1 00	2 29	4 94	1 02
Beans, str	2 32	2 57	1 37	2 28	2 52	1 38
Tomato	1 12	1 21	0 69	1 10	1 23	0 66
Potato	0 71	0 91	0 49	0 71	0 88	0 49
Onion	3 72	5 38	1 96	3 87	5 38	2 16

[a] All values given are averages of closely agreeing replicates
[b] Official method of analysis of the Association of Official Agricultural Chemists 6 74 (1955)
[c] 6 75 (1955)
[d] Calculated as invert sugar
[e] 29 64 and 29 65 (1955)

*Data from Western Utilization Research and Development Division, U S Dept of Agriculture, Agricultural Research Service, through James R Wilson, M D

APPENDIX C

TABLE 147.—HEIGHTS AND WEIGHTS OF CHILDREN BETWEEN ONE AND FOUR YEARS OF AGE (WITHOUT CLOTHES)[1]

5002 boys			4821 girls	
Height, inches	Weight, pounds	Age, months	Height, inches	Weight, pounds
26.5	18.0	6	25.9	16.8
27.3	19.1	7	26.5	17.4
27.6	19.8	8	27.0	18.3
28.1	20.4	9	27.6	19.1
28.5	20.9	10	27.9	19.5
29.0	21.4	11	28.4	20.1
29.4	21.9	12	28.9	20.8
29.9	22.9	13	29.4	21.0
30.3	23.0	14	29.5	21.6
30.8	23.6	15	30.1	21.9
31.1	24.1	16	30.5	22.6
31.4	24.5	17	30.8	22.9
31.8	24.6	18	31.1	23.4
32.3	25.5	19	31.5	23.8
32.6	25.8	20	32.0	24.1
32.9	25.8	21	32.3	24.8
33.3	26.9	22	32.6	25.3
33.6	27.0	23	32.9	25.6
33.8	27.1	24	33.4	26.4
34.0	27.9	25	33.8	26.9
34.1	28.3	26	33.9	27.3
34.8	29.0	27	33.9	27.3
35.1	29.1	28	34.6	27.8
35.4	29.3	29	34.8	27.8
35.4	29.5	30	34.9	28.3
35.5	30.5	31	35.1	28.8
36.0	30.6	32	35.4	29.0
36.1	30.6	33	35.6	29.1
36.5	31.1	34	36.5	30.1
36.8	31.9	35	36.5	30.3
37.1	32.3	36	36.8	30.5
37.4	32.3	37	36.8	30.8
37.5	32.4	38	37.0	31.0
37.9	33.1	39	37.3	31.6
38.5	33.5	40	37.5	32.0
38.6	33.6	41	37.8	32.3
38.6	33.8	42	38.0	32.5
38.8	33.8	43	38.3	32.8
38.9	34.3	44	38.5	33.0
39.0	34.5	45	38.5	33.5
39.0	34.8	46	38.8	33.5
39.3	35.8	47	38.9	33.5
39.5	35.9	48	39.0	33.8

[1] Crum, I. S., Quarterly Publication of the American Statistical Association, Boston, September, 1916, N. S., No. 115, *15*: 332.

TABLE 148.—HEIGHTS AND WEIGHTS OF BOYS BETWEEN FIVE AND FOURTEEN YEARS (WITHOUT CLOTHES)[1]

BOYS

Weight in Pounds — Without Clothes

Height in Feet and Inches — Without Shoes

AGE	3-2	3-4	3-5	3-6	3-7	3-8	3-9	3-10	3-11	4	4-1	4-2	4-3	4-4	4-5	4-6	4-7	4-8	4-9	4-10	4-11	5	5-1	5-2	5-3	5-4	5-5	5-6	5-7	5-8	5-9	5-10	5-11	6	6-1
5	35	36	39	41	42	46																													
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

TABLE 149.—HEIGHTS AND WEIGHTS OF GIRLS BETWEEN FIVE AND FOURTEEN YEARS (WITHOUT CLOTHES)[1]

GIRLS

Weight in Pounds — Without Clothes

Height in Feet and Inches — Without Shoes

AGE	3-3	3-4	3-5	3-6	3-7	3-8	3-9	3-10	3-11	4	4-1	4-2	4-3	4-4	4-5	4-6	4-7	4-8	4-9	4-10	4-11	5	5-1	5-2	5-3	5-4	5-5
5	36	37	38	40	41	43																					
6		35	37	39	41	43	46	49																			
7				38	42	44	46	47	50																		
8						43	45	47	48	51	53	56															
9									49	51	53	56	58	60													
10											54	57	59	62	64	65											
11													60	62	65	66	70	73									
12														63	66	67	71	75	78	80	86	[illegible]					
13															65	69	73	78	80	86	89	94	98	104			
14																		78	84	88	93	98	100	104	107	112	116
15																				96	[illegible]	100	102	105	109	110	116
16																											

[1] Wood, T. D. The ninth yearbook of the National Society of the Study of Education, Part I. Health and Education. Chicago, 1910, p. 34.

TABLE 150.—HEIGHTS AND WEIGHTS OF 221,819 MEN OF FIFTEEN OR MORE YEARS OF AGE (WITH CLOTHES).[1]

Age	Graded average weight in pounds with clothes. Feet and inches with shoes: 5-0	5-1	5-2	5-3	5-4	5-5	5-6	5-7	5-8	5-9	5-10	5-11	6-0	6-1	6-2	6-3	6-4	6-5
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
30	126	128	130	133	136	140	144	148	152	156	161	166	172	178	184	190	196	201
31	127	129	131	134	137	141	145	149	153	157	162	167	173	179	185	191	197	202
32	127	129	131	134	137	141	145	149	154	158	163	168	174	180	186	192	199	203
33	127	129	131	134	137	141	145	149	154	159	164	169	175	181	187	193	190	204
34	128	130	132	135	138	142	146	150	155	160	165	170	176	182	188	194	200	206
35	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	207
36	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
37	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
38	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
39	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
55	135	137	139	142	145	149	153	158	163	168	173	178	184	191	198	205	212	219

[1] Association of Life Insurance Directors and Actuarial Society of America, New York, 1912, p 38 Published by a committee Allow 1 inch for shoes and 10 pounds for clothes

TABLE 151.—HEIGHTS AND WEIGHTS OF 136,504 WOMEN OF FIFTEEN OR MORE YEARS OF AGE (WITH CLOTHES)[1]

Age	Graded average weight in pounds with clothes																
	Feet and inches with shoes																
	4-8	4-9	4-10	4-11	5-0	5-1	5-2	5-3	5-4	5-5	5-6	5-7	5-8	5-9	5-10	5-11	6-0
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
55	123	127	129	131	133	135	138	141	144	149	153	158	163	167	171	174	177

[1] Association Life Insurance Directors and Actuarial Society of America New York 1912 p 67 Published by a committee Allow 1½ inches for shoes and 6 pounds for clothes

Table 152.—Desirable Weights for Men of Ages 25 and Over

Weight in Pounds According to Frame (as ordinarily dressed)

Height (with shoes on) Feet	*Inches*	*Small Frame*	*Medium Frame*	*Large Frame*
5	2	116–125	124–133	131–142
5	3	119–128	127–136	133–144
5	4	122–132	130–140	137–149
5	5	126–136	134–144	141–153
5	6	129–139	137–147	145–157
5	7	133–143	141–151	149–162
5	8	136–147	145–156	153–166
5	9	140–151	149–160	157–170
5	10	144–155	153–164	161–175
5	11	148–159	157–168	165–180
6	0	152–164	161–173	169–185
6	1	157–169	166–178	174–190
6	2	163–175	171–184	179–196
6	3	168–180	176–189	184–202

Table 153.—Desirable Weights for Women of Ages 25 and Over

Weight in Pounds According to Frame (as ordinarily dressed)

Height (with shoes on) Feet	*Inches*	*Small Frame*	*Medium Frame*	*Large Frame*
4	11	104–111	110–118	117–127
5	0	105–113	112–120	119–129
5	1	107–115	114–122	121–131
5	2	110–118	117–125	124–135
5	3	113–121	120–128	127–135
5	4	116–125	124–132	131–142
5	5	119–128	127–135	133–145
5	6	123–132	130–140	138–150
5	7	126–136	134–144	142–154
5	8	129–139	137–147	145–158
5	9	133–143	141–151	149–162
5	10	136–147	145–155	152–166
5	11	139–150	148–158	155–169

These tables are based on numerous Medico-Actuarial studies of hundreds of thousands of insured men and women

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